Aging & Rehabilitation

An Interdisciplinary Research Seminar Series

Sponsors

Department of Veteran Affairs

- Rehabilitation Outcomes Research Center (RORC)
- Brain Rehabilitation Outcomes Research Center (BRRC)
- Geriatric Research, Education, and Clinical Center (GRECC)

UF College of Medicine

- Institute on Aging
- Department of Aging and Geriatric Research

UF College of Public Health and Health Professions

- **Brooks Center for Rehabilitation Studies**

UF College of Liberal Arts and Sciences

- Center for Gerontological Studies

UF McKnight Brain Institute

UF College of Nursing

Schedule

- January 9th, 2006 – May 22nd, 2006
- Mondays, 12:00 – 1:00
- Location: UF HPNP Building, Room G101
- Cyber Seminar:
  - VA RORC Conference Room, Commerce Building Downtown
  - VA BRRC Nursing Home Care Unit Conference Room (first floor)
  - UF Brooks Center Conference Room, Jacksonville (904) 306-8977

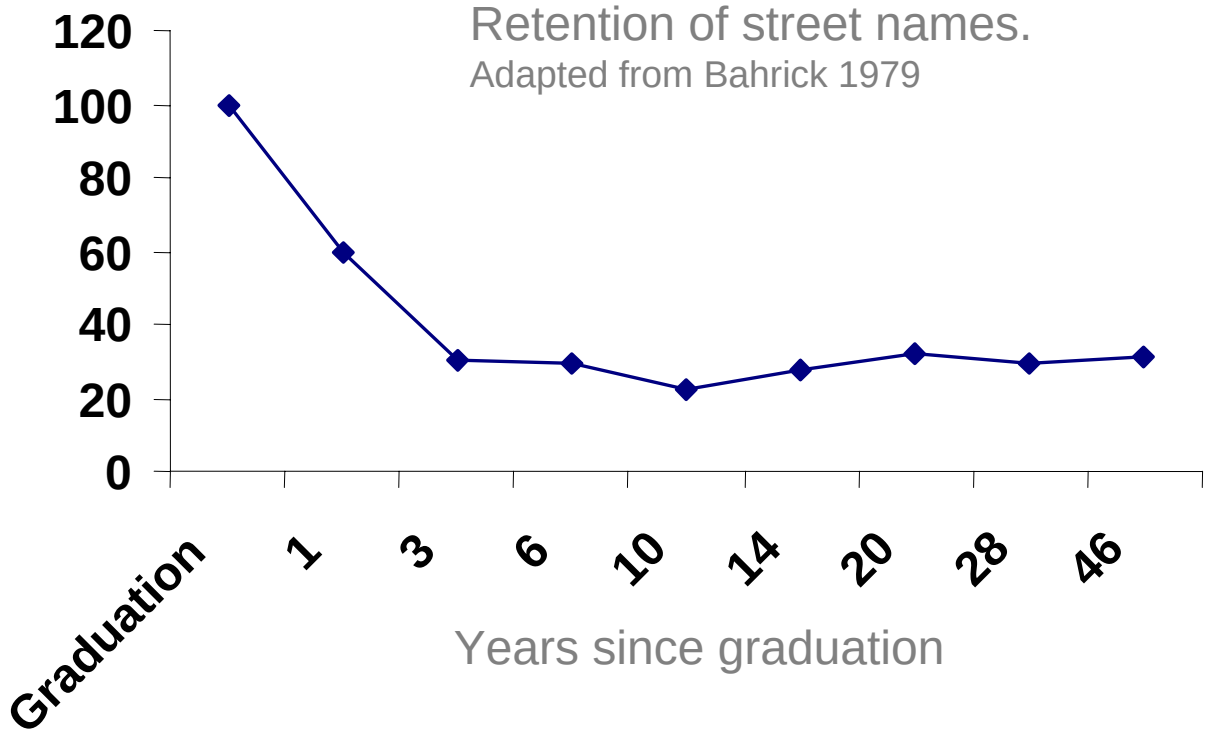
Themes

- Basic Science
- Clinical Science
- Outcomes / Health Policy
- Behavioral and Social Research
- Cutting Edge / New Research

Educational Objectives:

- 1) To understand how changes in episodic memory constitute a memory disorders, with a focus on age-related decline in episodic memory.
- 2) To have a basic knowledge of the biological basis of memory with an emphasis on the anatomical substrates.
- 3) To have a basic knowledge of some biological markers of brain aging that correlated with memory decline.

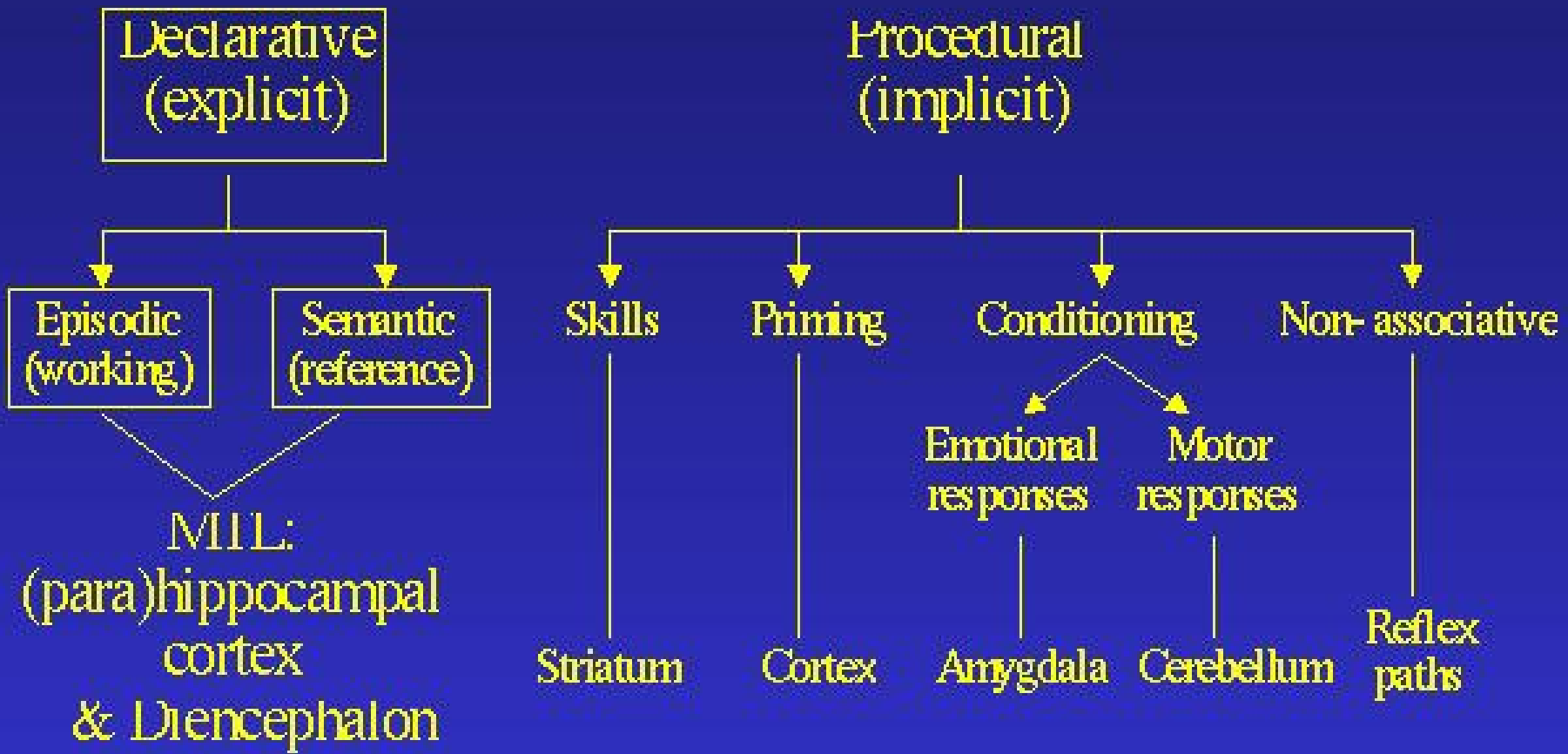
Remote memory is relatively intact in older individuals



Composer Aaron Copland in describing the problems he encountered while writing his autobiography.

“I have no trouble remembering everything that happened 40 or 50 years ago – dates, places, faces, music. But I’m going to be 90 my next birthday, Nov. 14th, and I find that I can’t remember what happened yesterday.”

Taxonomy of Memory

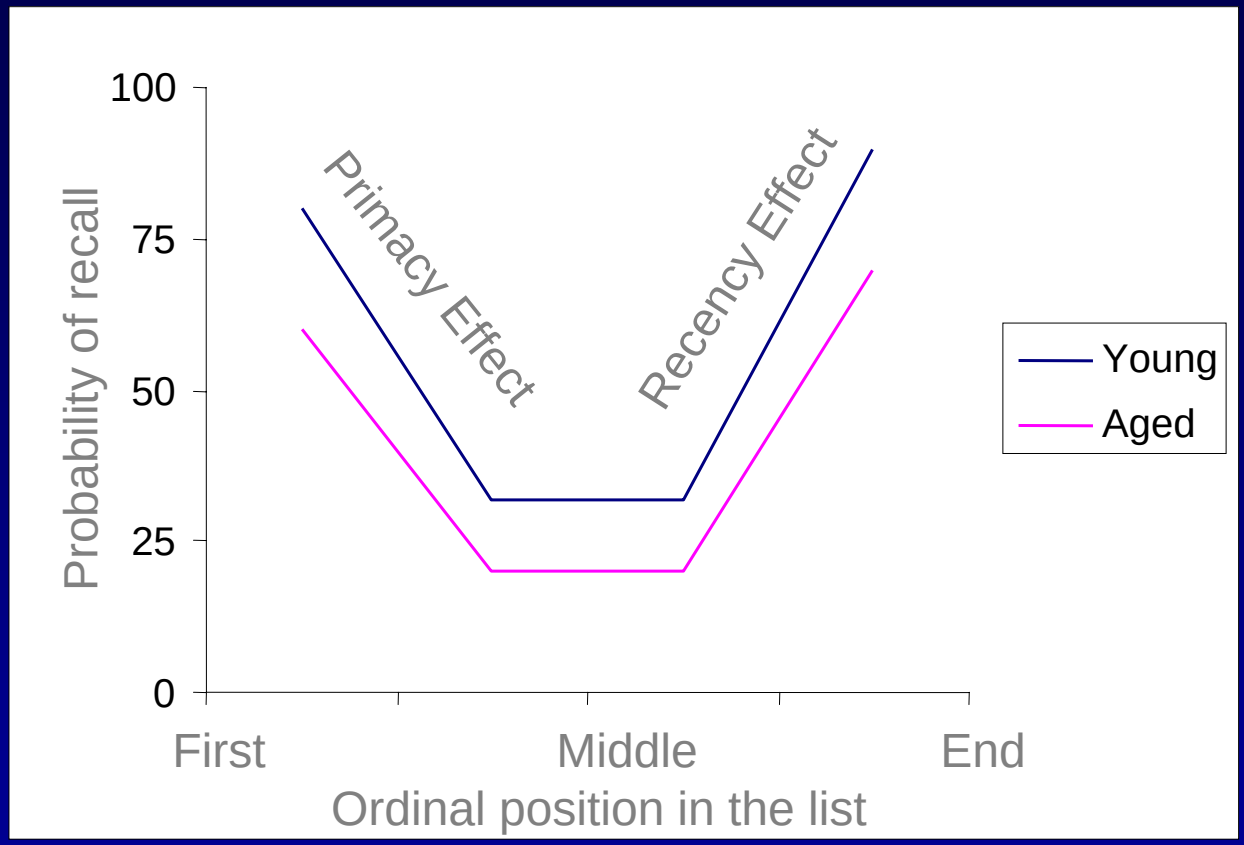


(Adapted from L.R. Squire: "Memory and the Brain", 1987)

Declarative, episodic or explicit memory:

Memory for facts, life events; can be accessed for conscious recollection; easy to form, easily forgotten. Relational learning - the linking together of stimuli, context and events - involves a significant temporal component.

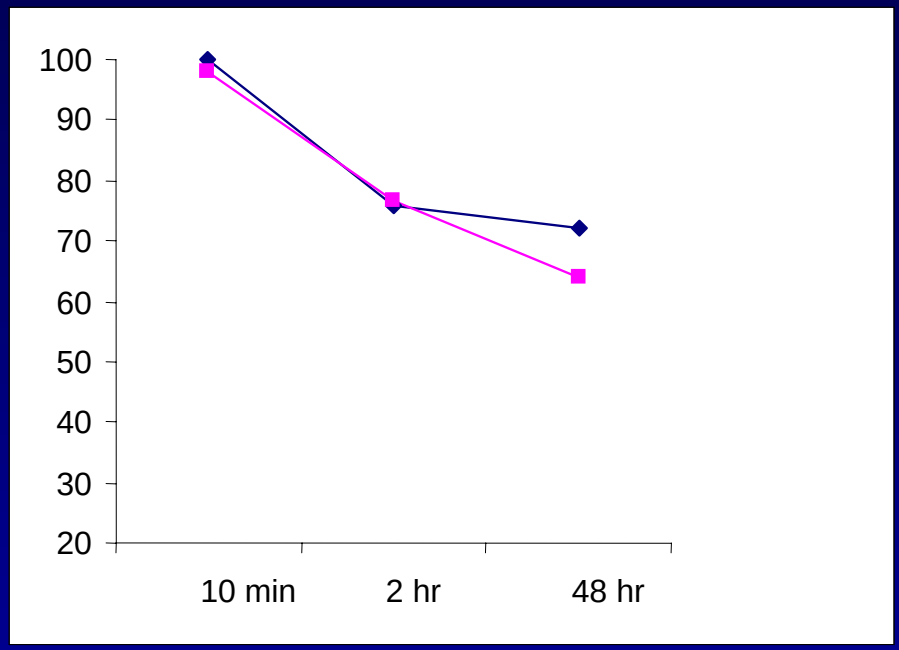
Primacy and recency effects in recall of items from free-recall lists



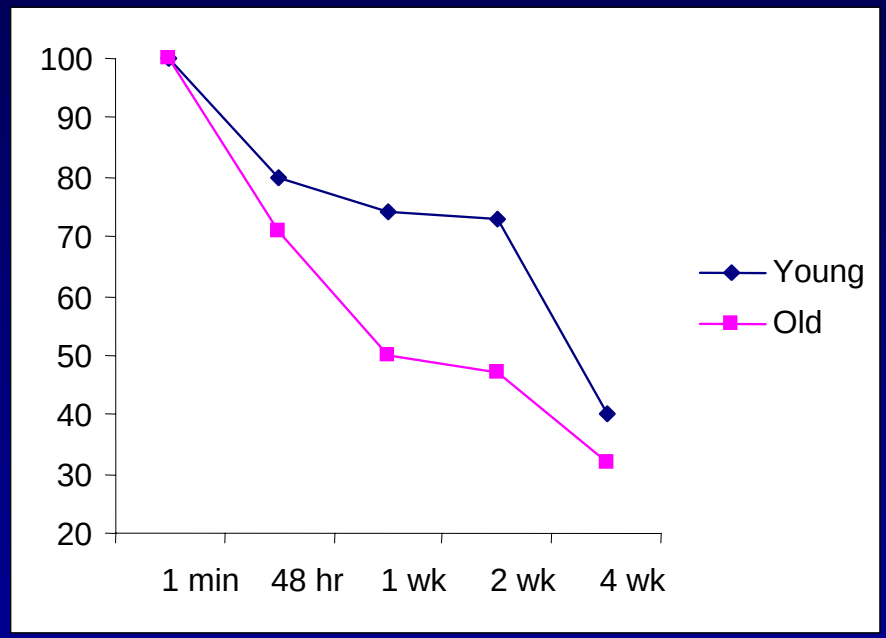
Arenberg 1976

The problem appears to be slower encoding by aged individuals.

Forgetting curves for pictorial material:



Adapted from Rybarczyk et al, 1987

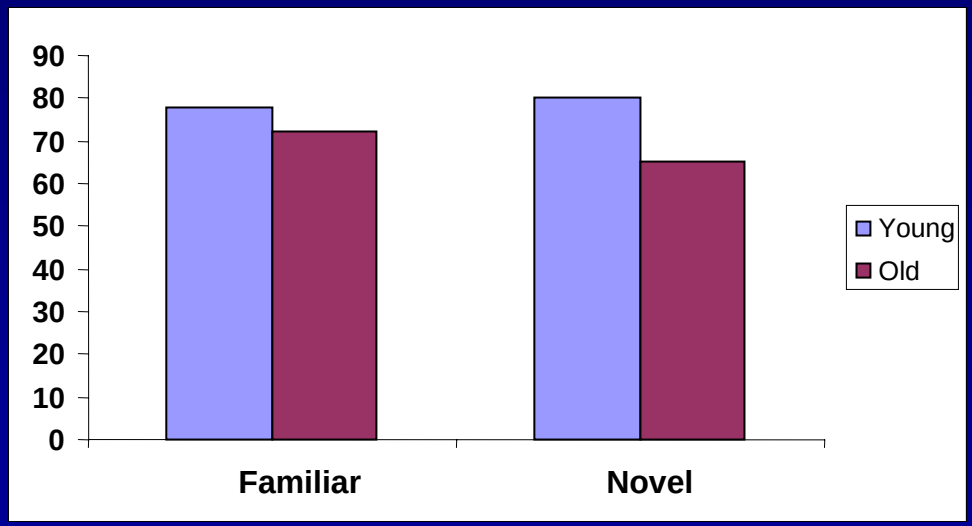


Adapted from Park et al, 1988

Aging is associated with deficits in consolidation or rapid forgetting.

AREA	Mean % correct identification Elderly	Students
Hall 1	12	48
Hall 2	5	28
Hall 3	4	20
Hall 4	13	33
Dinning Room	61	81
Lobby	52	85
Exterior	33	48

Weber et al, 1978



Recognition of supermarket picture (Kirasic 1991)

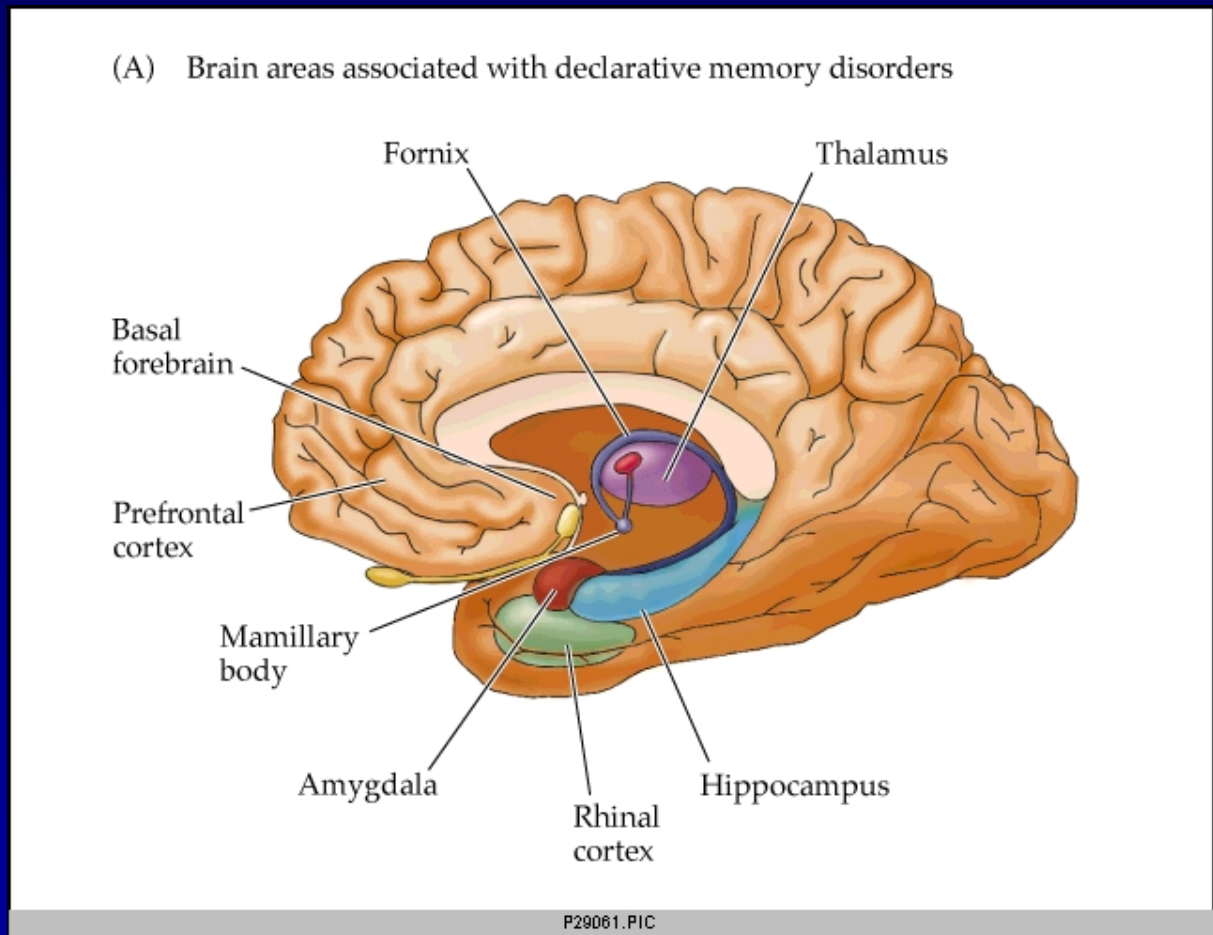
Both the ability to acquire novel spatial information and the ability to retain long-standing spatial information appear to be highly age-sensitive processes (D. H. Kausler Learning and Memory in Normal Aging, 1994).

The Case of H.M.

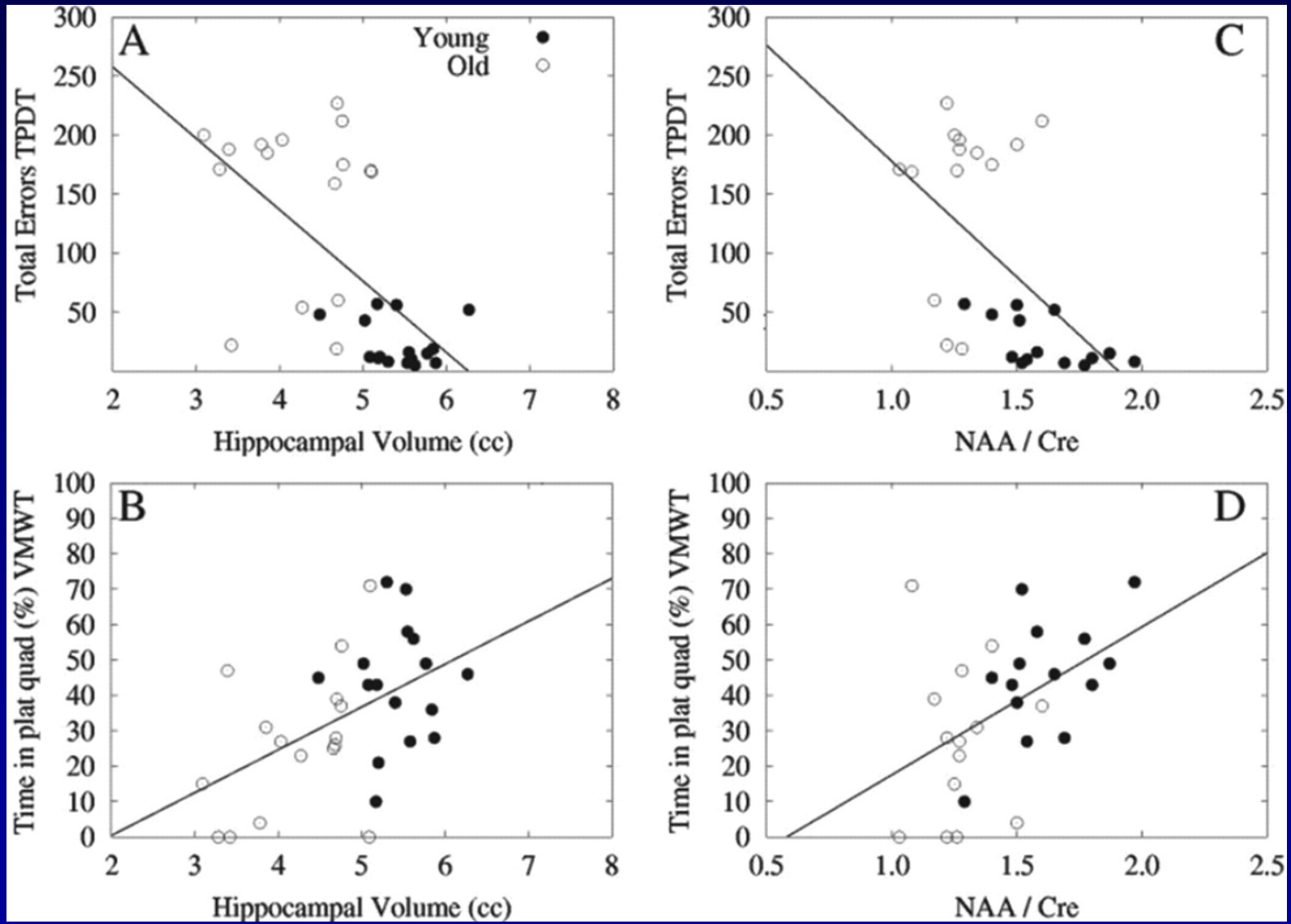
Bilateral medial temporal lobectomy (amygdala, uncus, and anterior 2/3 of **hippocampus** were removed)

Successful operation in some respects:
a) convulsions reduced in frequency and severity
b) I.Q. increased from around 104 to 118
c) emotionally stable

BUT HIS DECLARATIVE MEMORY WAS SEVERELY IMPAIRED



Memory decline is associated with decreased hippocampal volume



Driscoll et al, 2003

The Aging Brain

Cognitive decline during normal aging is not associate with a loss of neurons.
Morrison & Hof, 2002.

Aging is associated with a decrease in brain volume and a loss of dendritic spines in some brain regions.

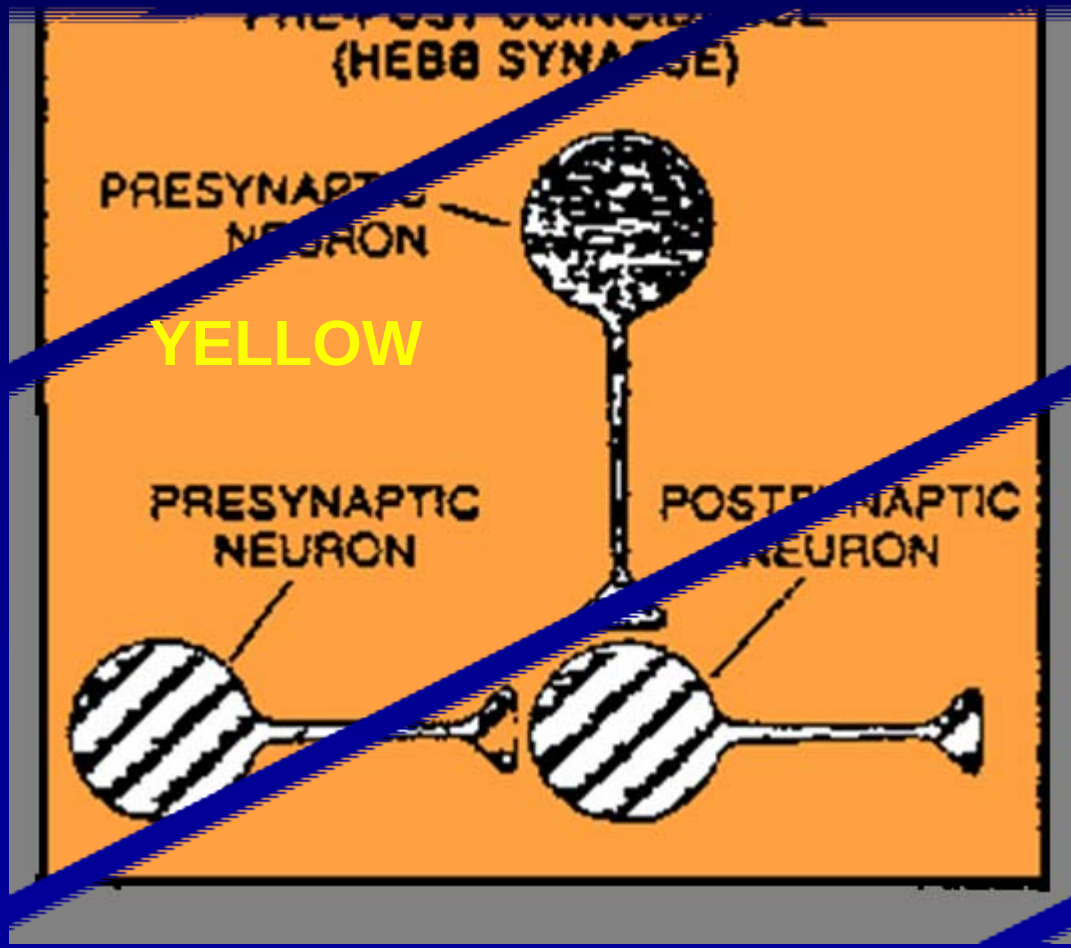
What are memory traces?

Memory traces are physical changes in the brain (e.g. synaptic contacts) for circuits of neurons that process information.

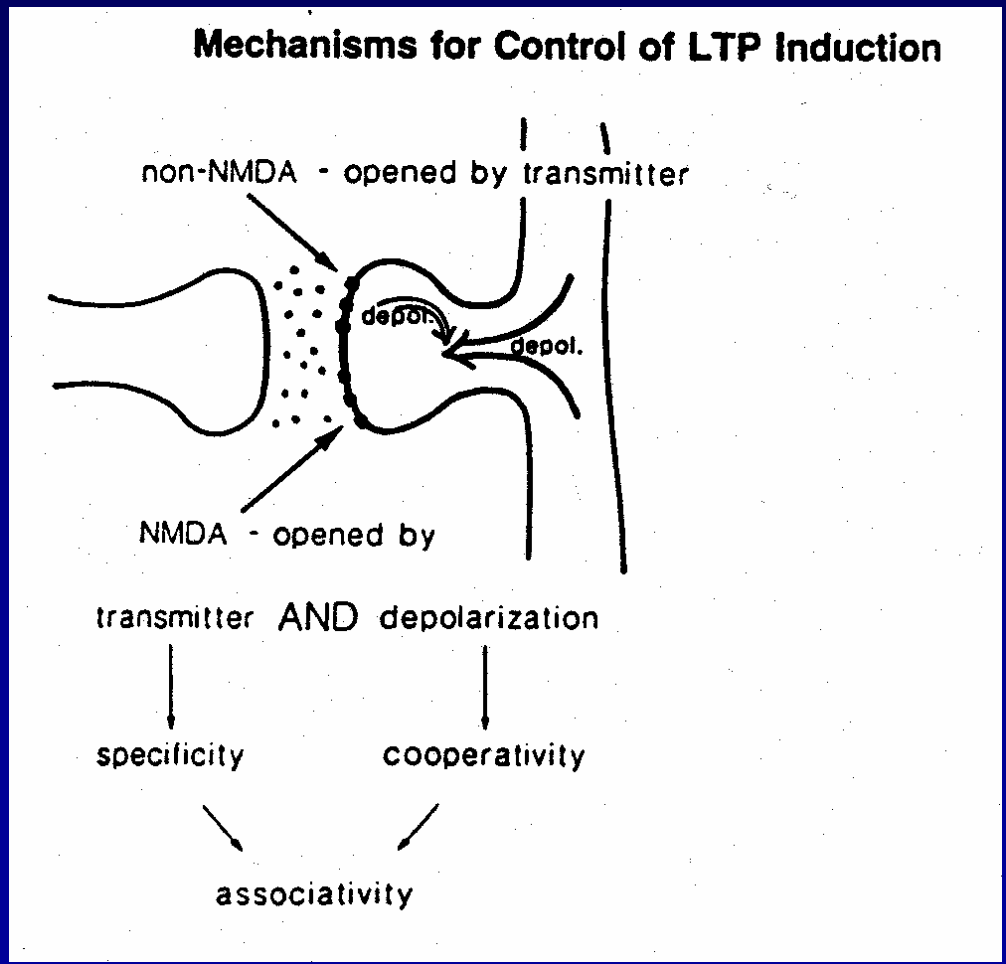
Donald O. Hebb in 1949, posits that <u>coincident</u> activity in the presynaptic and postsynaptic neurons is critical for strengthening the connections between them.

What do you think of when I say YELLOW?

YELLOW CHAIR



Long-term potentiation (LTP) is associative. Induction requires presynaptic activity (transmitter release) and postsynaptic activity (depolarization).

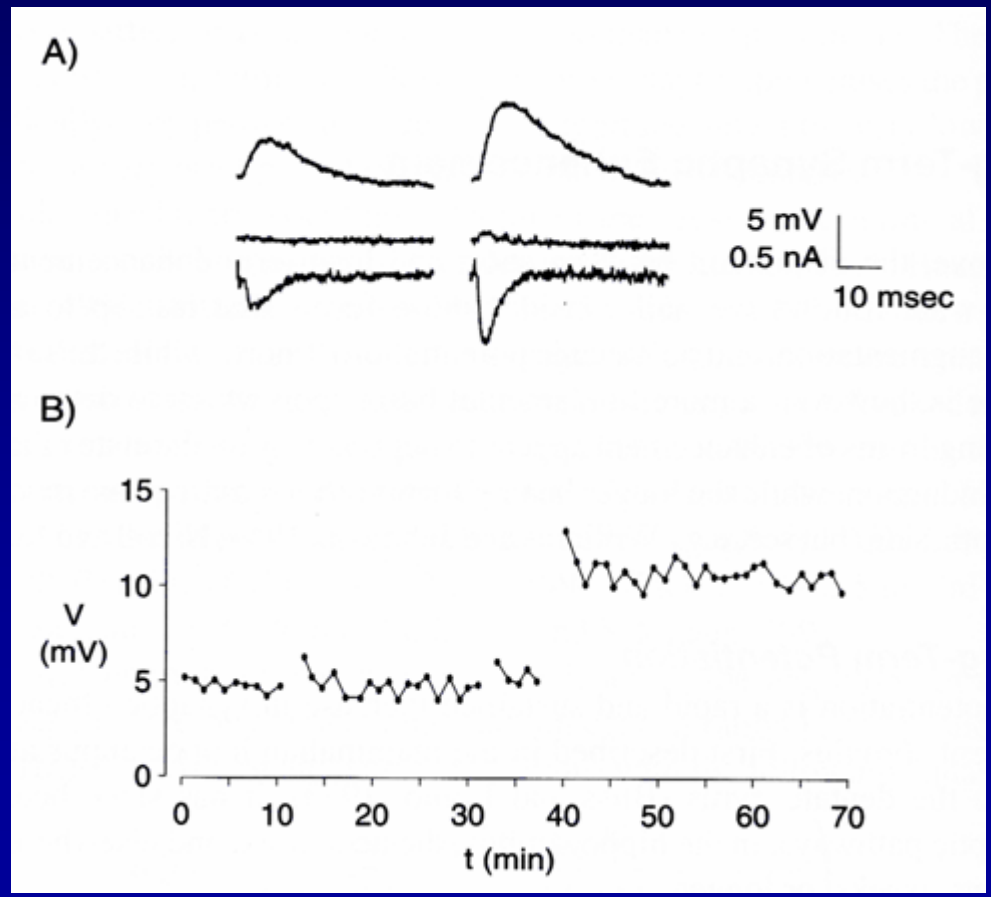


Long-term potentiation (LTP)

LTP is an increase in synaptic transmission.

Treatments that block LTP block memory (PCP, ethanol).

It is long lasting (months) and it show specificity**:**
Cells that fire together, wire together

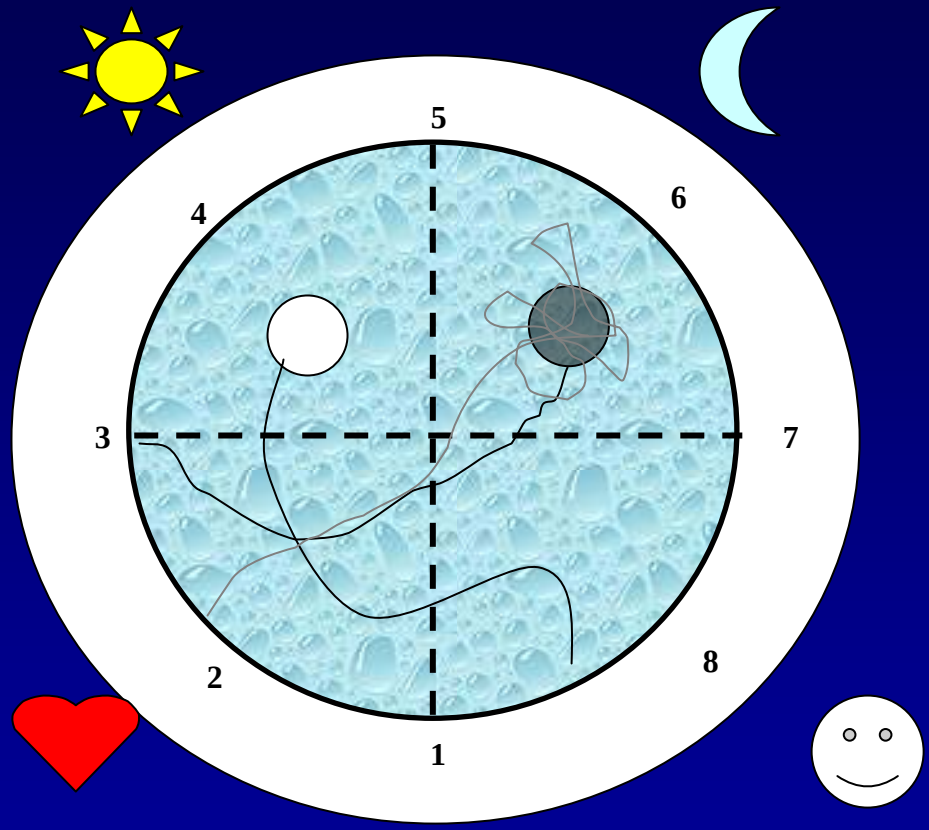


Molecular mechanisms of LTP

- NMDA-channel activation due to transmitter binding and release of Mg2+ block of the channel
- Rise in post-synaptic calcium
- Activation of kinases (CAMKII PKA and PKC)
- Phosphorylation of glutamate receptors increase current. Activation of cAMP-responsive element-binding proteins (CREB)
- Gene transcription
- Structural changes in the synapse

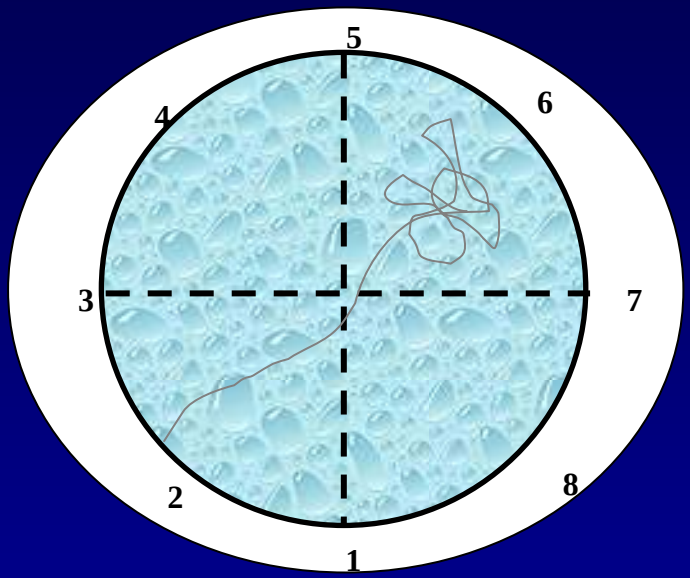
Animals are tested for sensory motor deficits

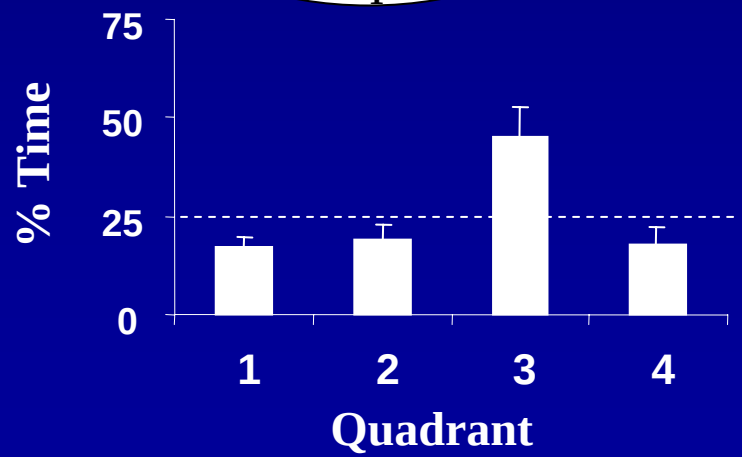
Animals are trained on a spatial learning task

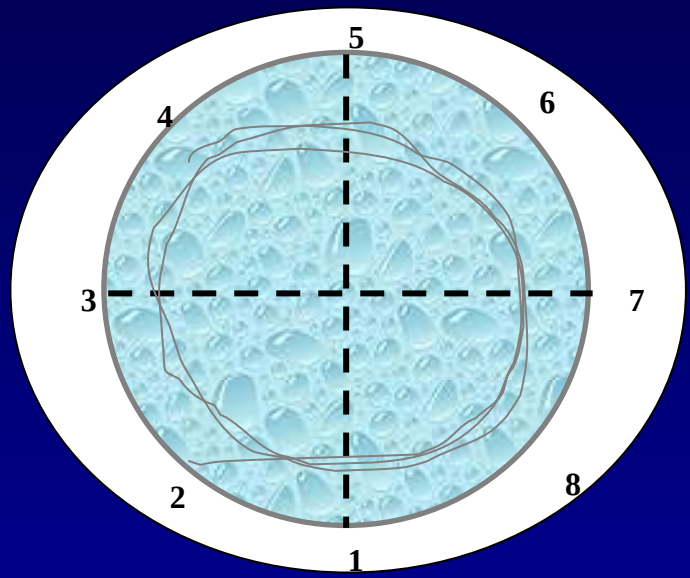


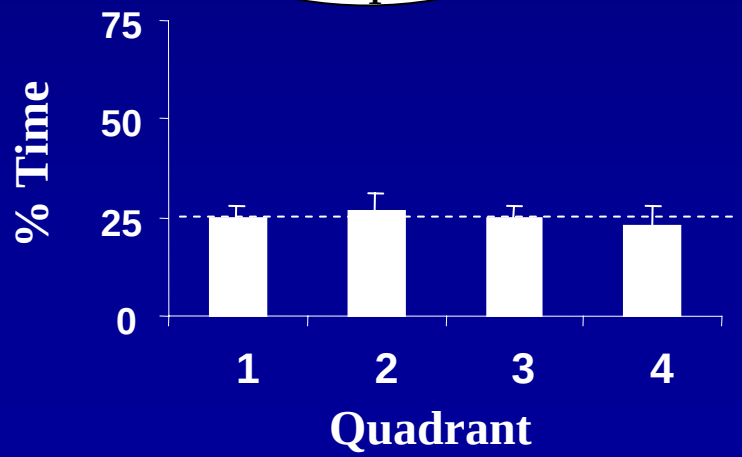
Animals are tested for spatial learning and memory

Learning without a hippocampus

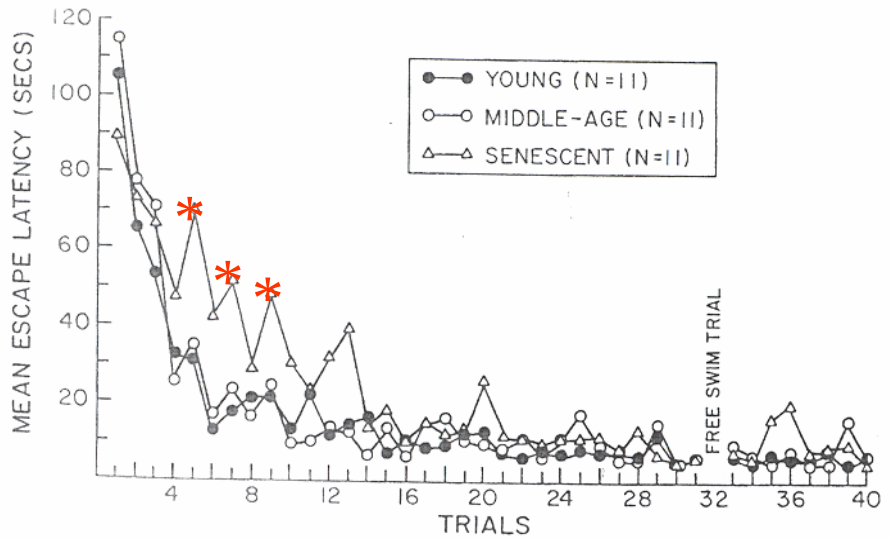




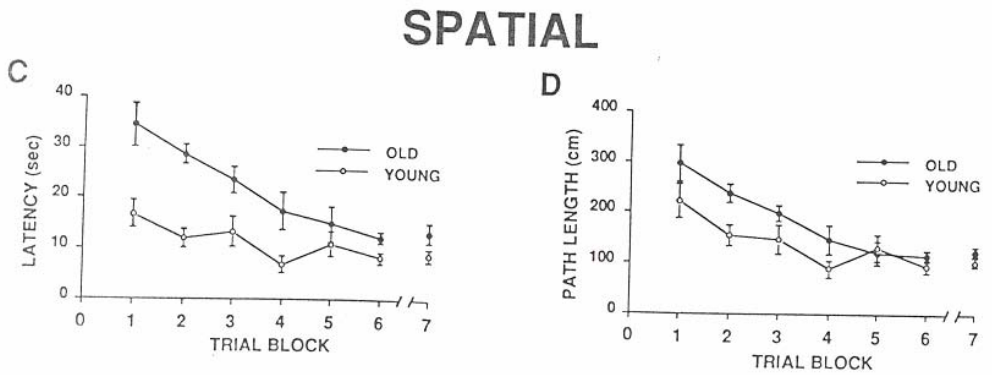




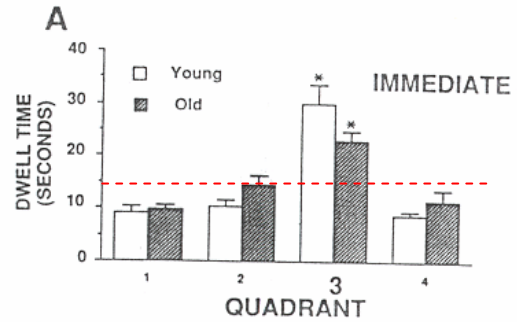
Aging is associated with impaired memory for hippocampal-dependent tasks



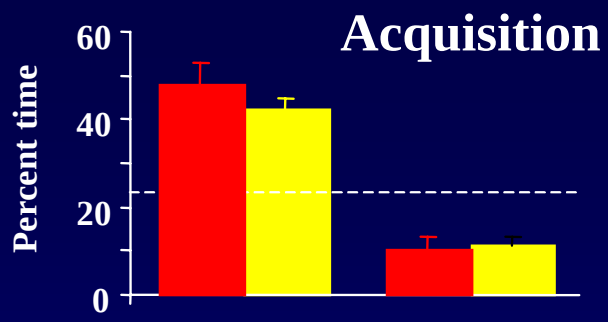
Rapp etal. 1987. Behavorial Neuroscience. 101, 3-13.

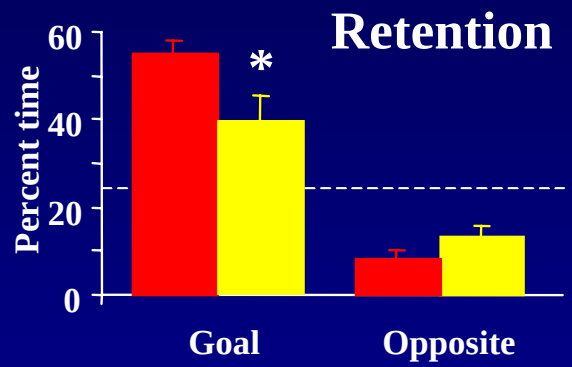


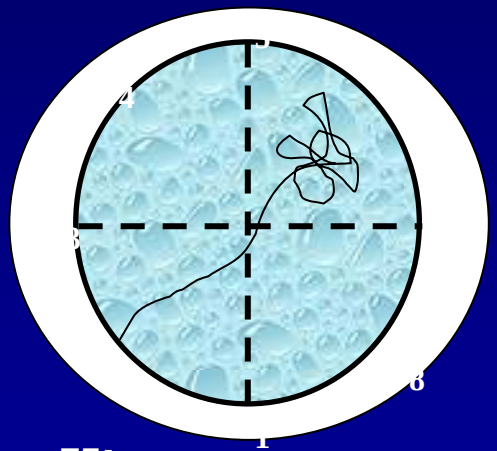
Foster et al. 1991. Neurobiology of Aging. 12, 441-448.

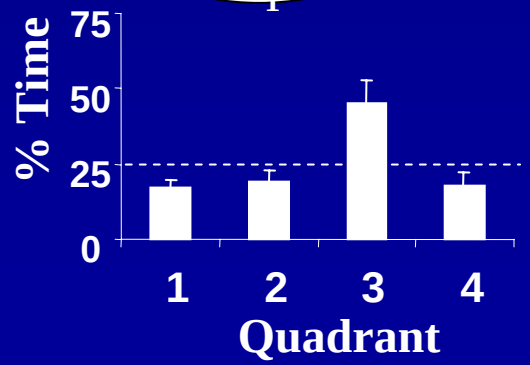


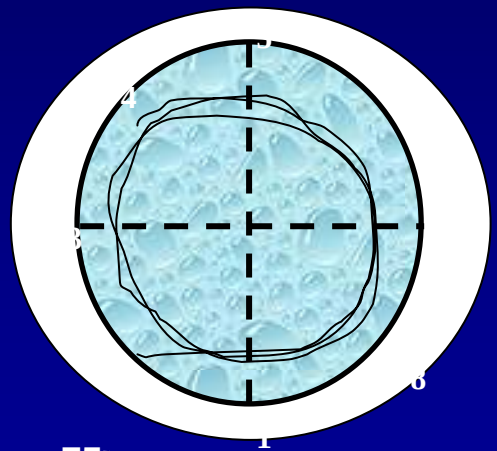
Age-related memory decline is variable

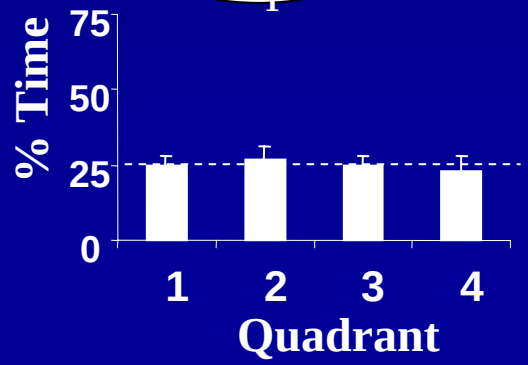


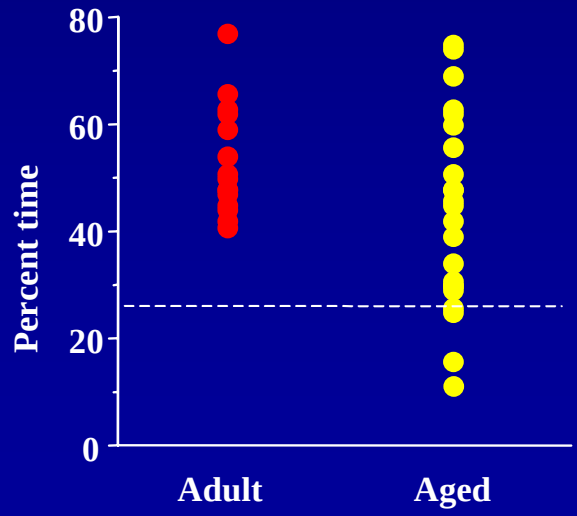




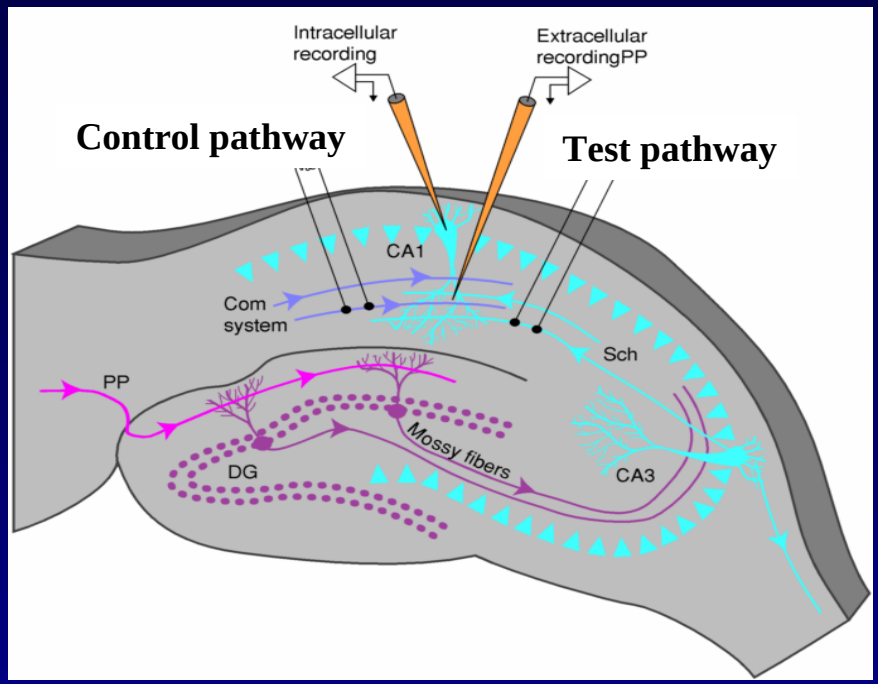


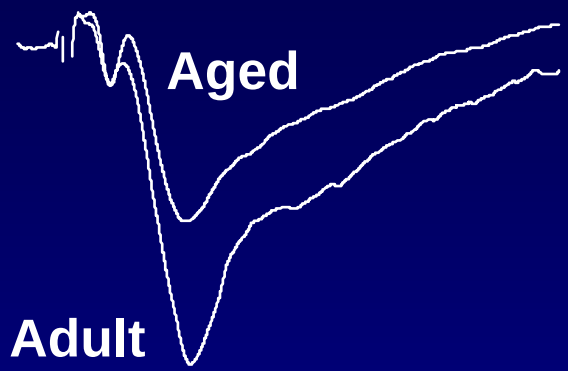


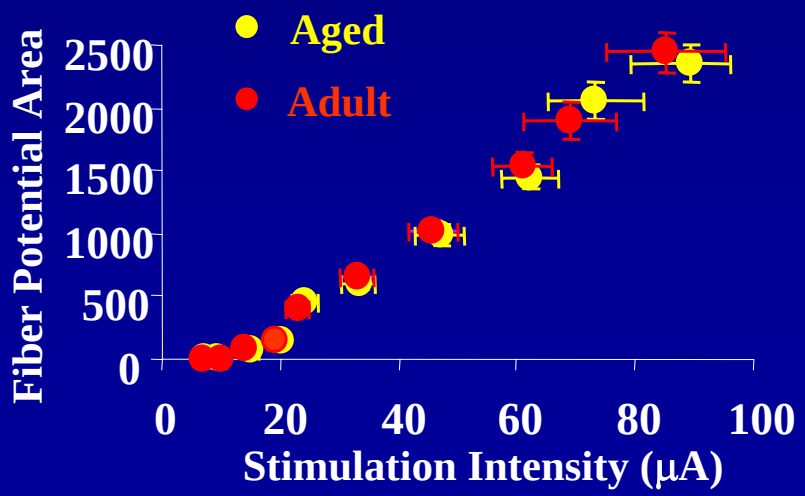


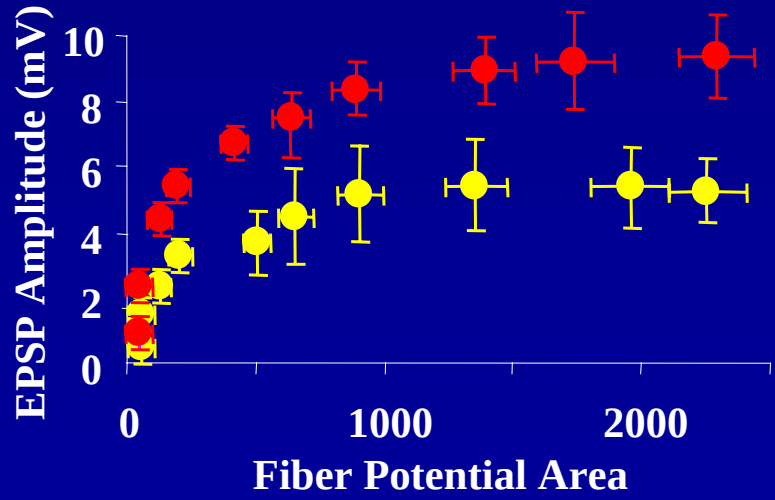


Reduced synaptic strength is a marker of aging

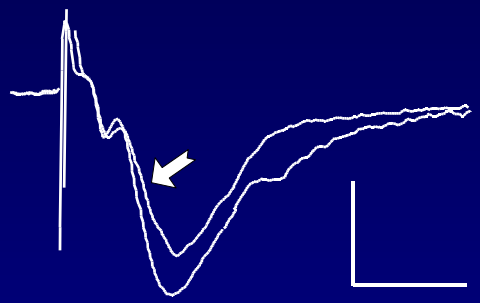


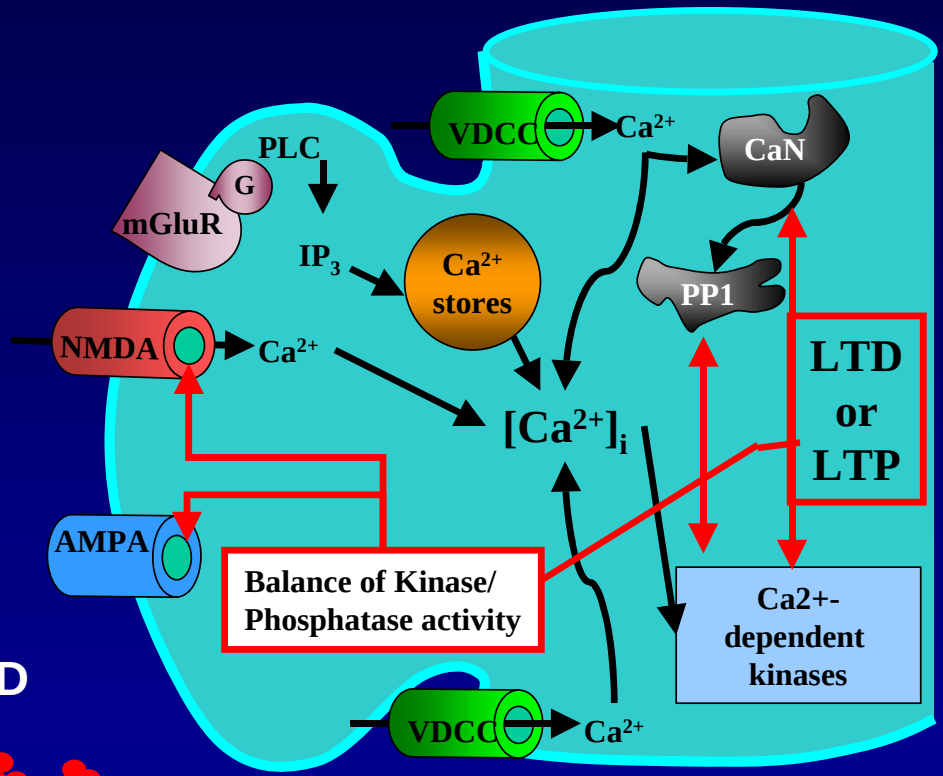


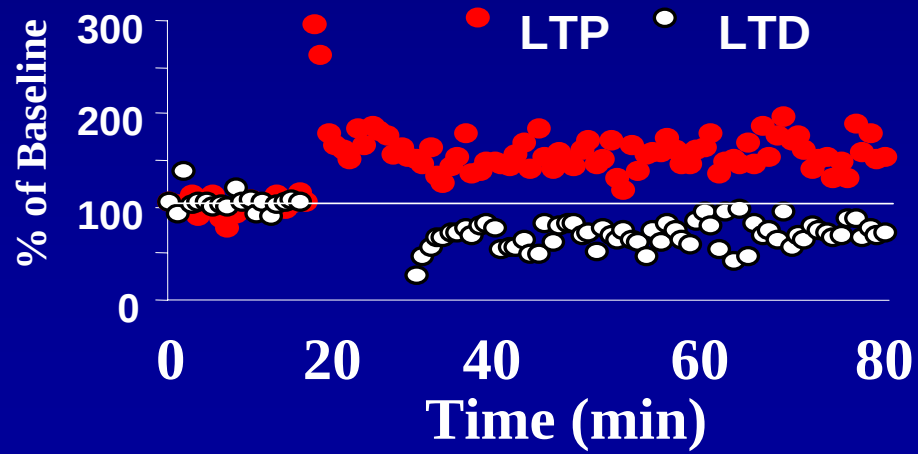




Hypothesis: The age-related decrease in synaptic strength is due to a shift in the balance of Ca^{2+}-dependent synaptic plasticity

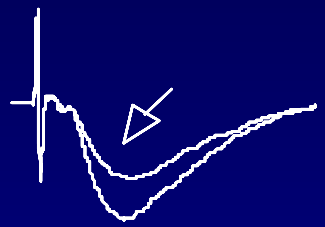




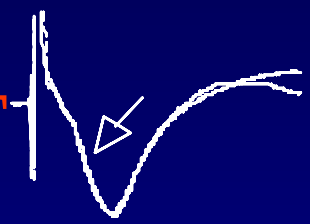


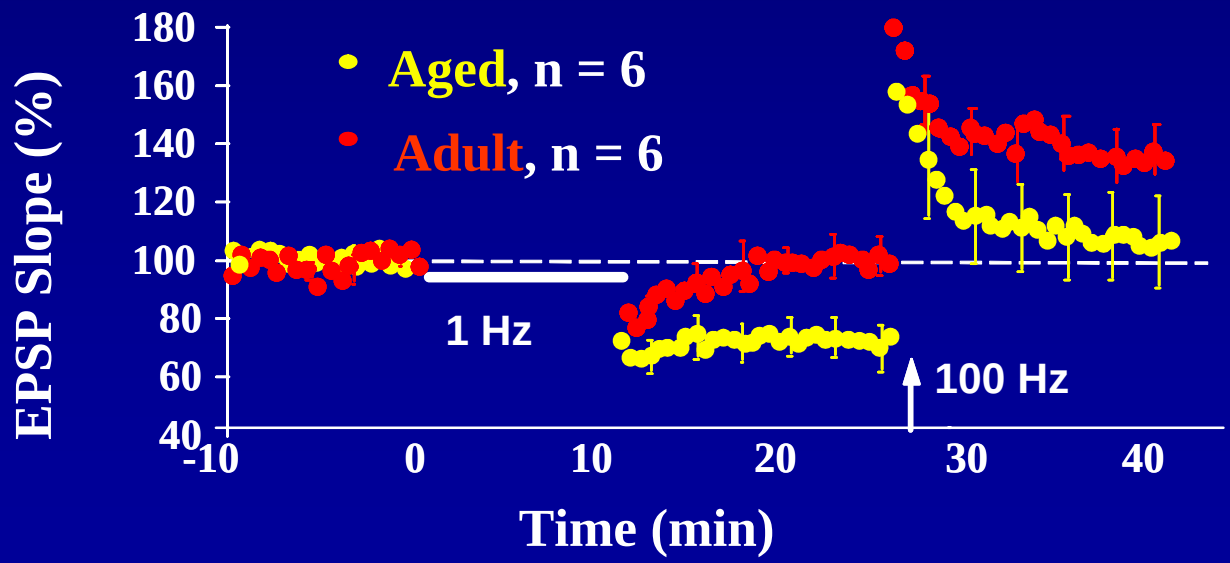
Increased Susceptibility to Synaptic Depression During Aging

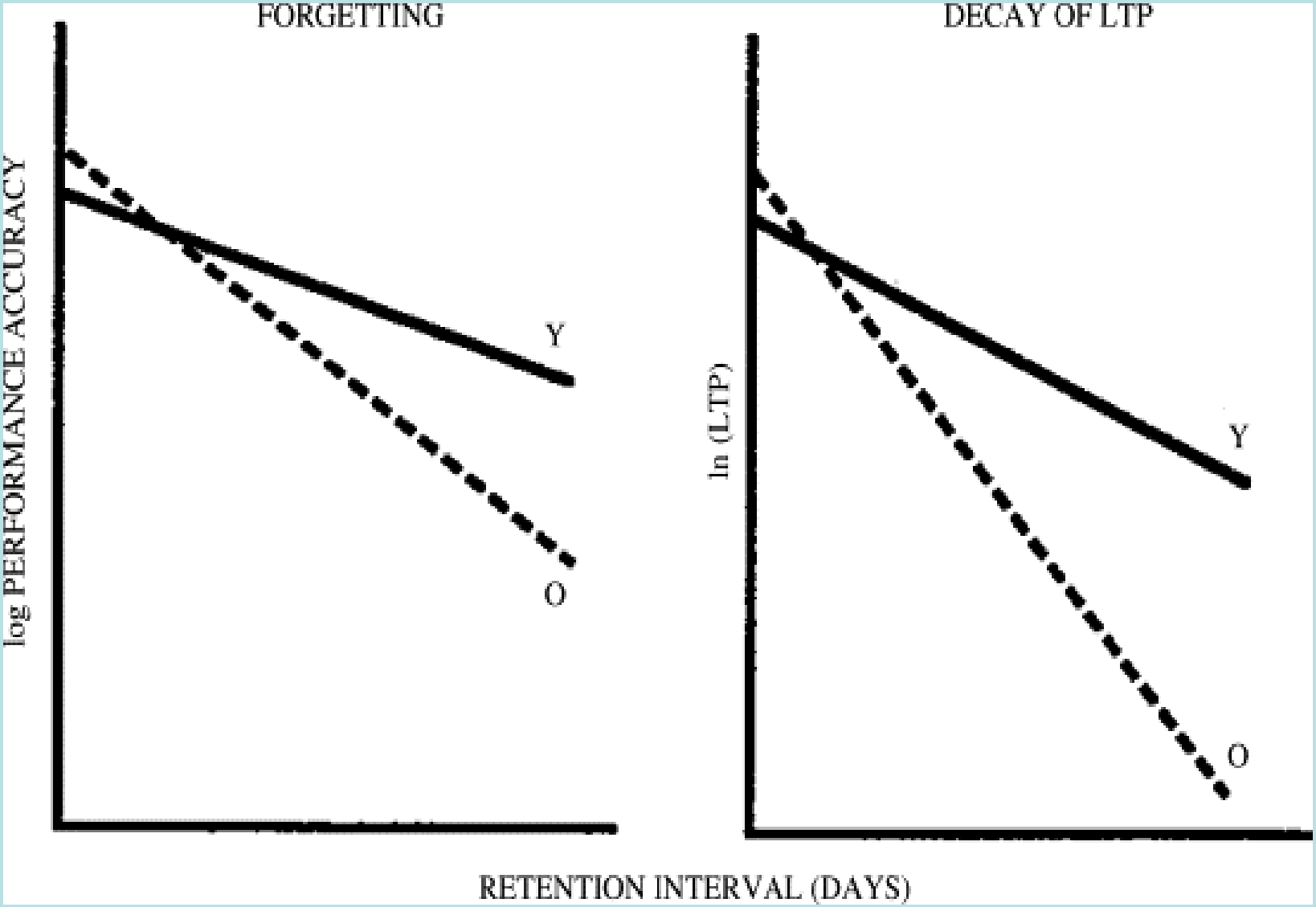
AGED

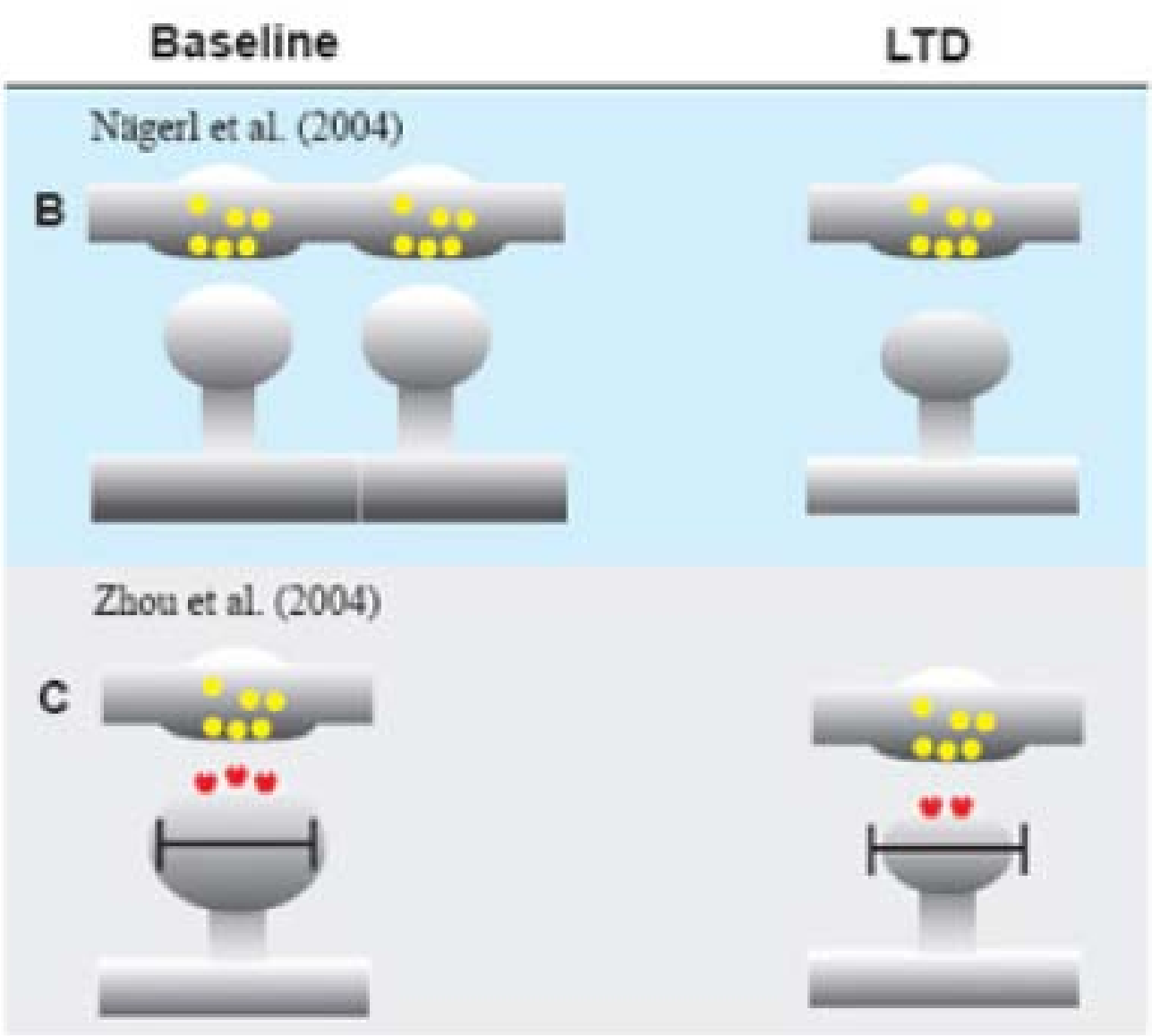


ADULT






FORGETTING
DECAY OF LTP
log PERFORMANCE ACCURACY
ln (LTP)
Y
O
Y
O
RETENTION INTERVAL (DAYS)


Baseline
LTD
Nägerl et al. (2004)
B
Zhou et al. (2004)
C

MEMORY CONSOLIDATION

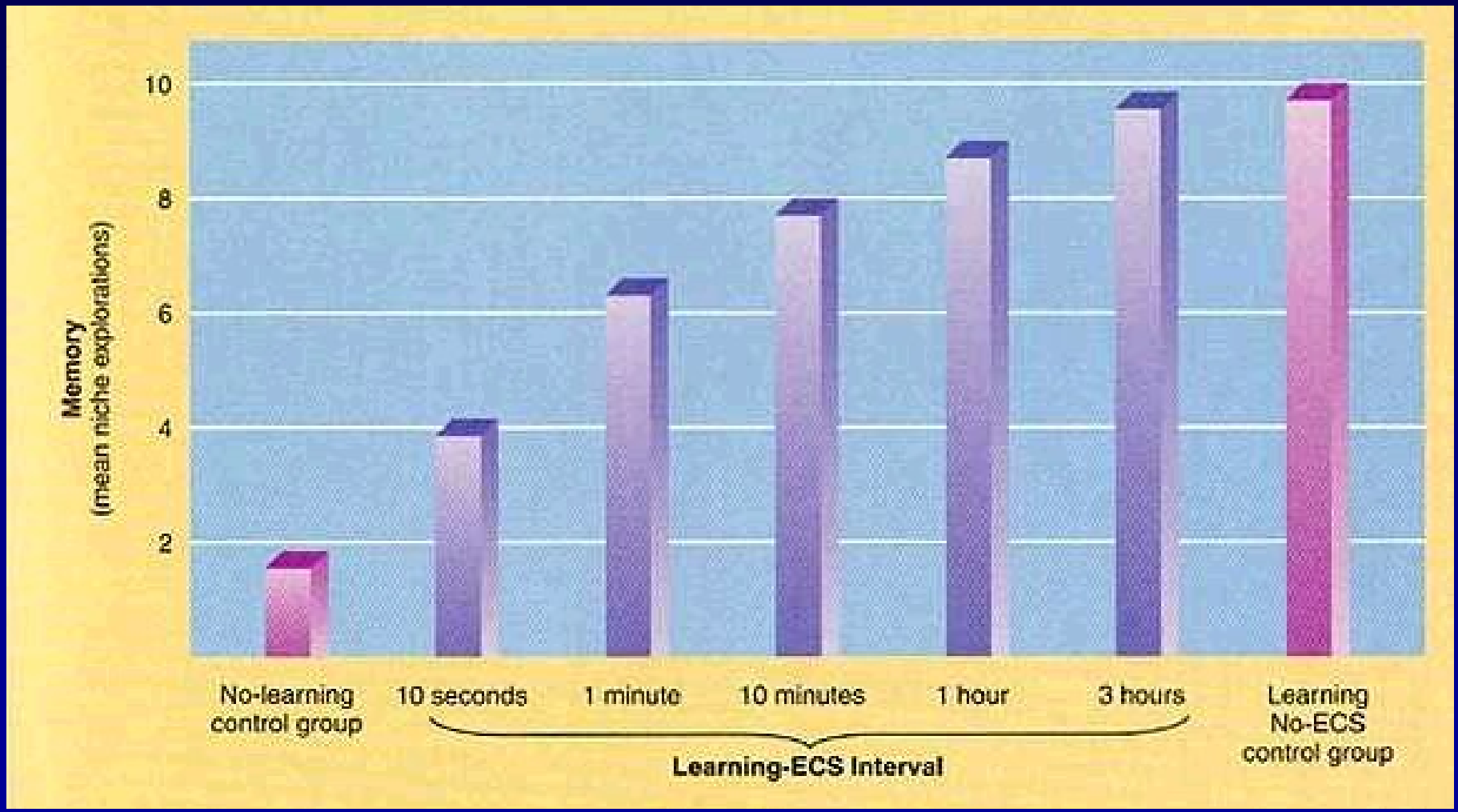
A fundamental property of long-term memory (LTM) is that it is labile shortly after information is acquired and becomes progressively more stable over time, a phenomenon known as **memory consolidation**.

The time window appears to be about 3 hrs, which is a rough estimate of STM and LTM.

RNA and Protein synthesis inhibitors

ECS studies

Time dependent disruption of memory by ECS

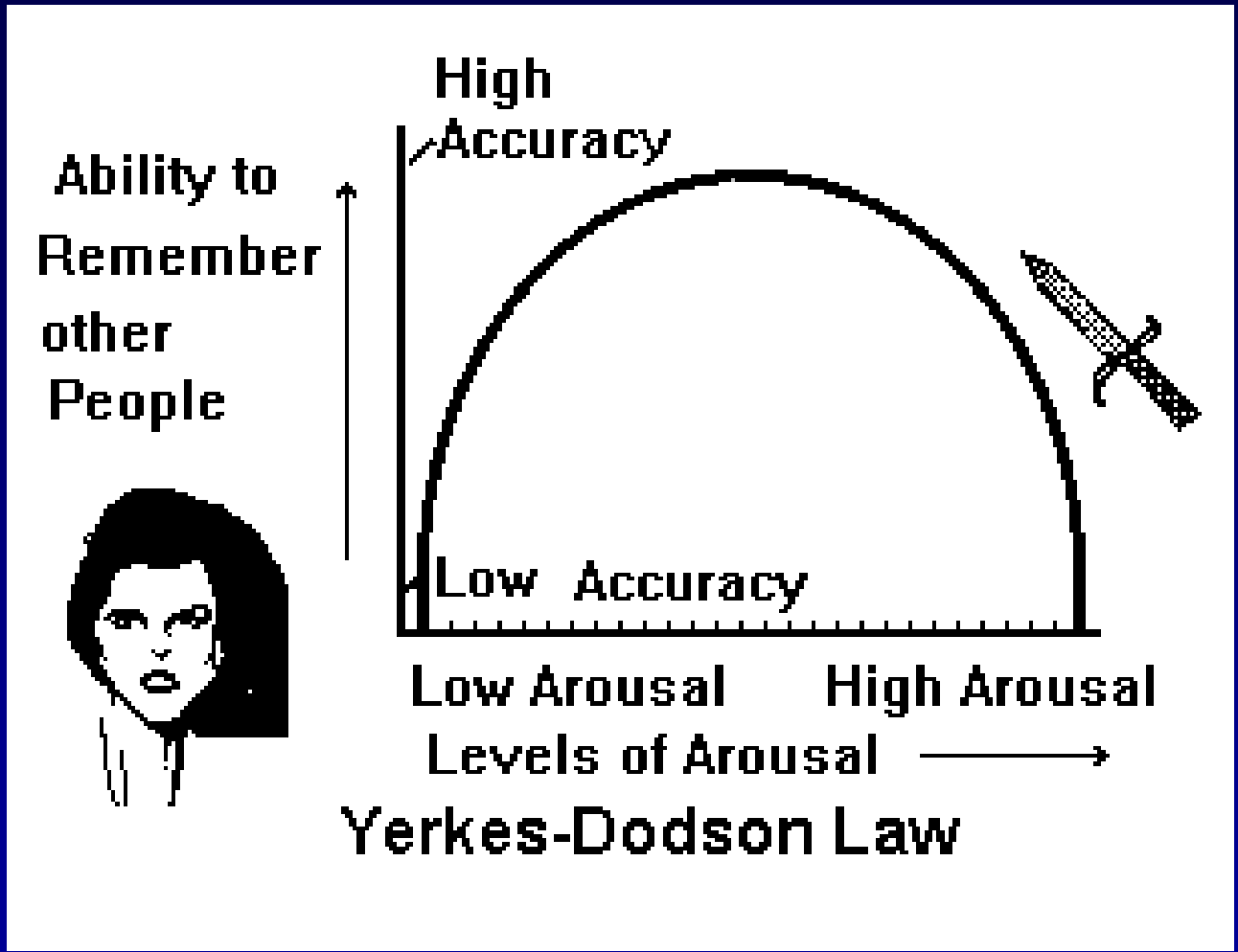


Flashbulb memories

More facts of nature: All forest animals, to this very day, remember exactly where they were and what they were doing when they heard that Bambi's mother had been shot.

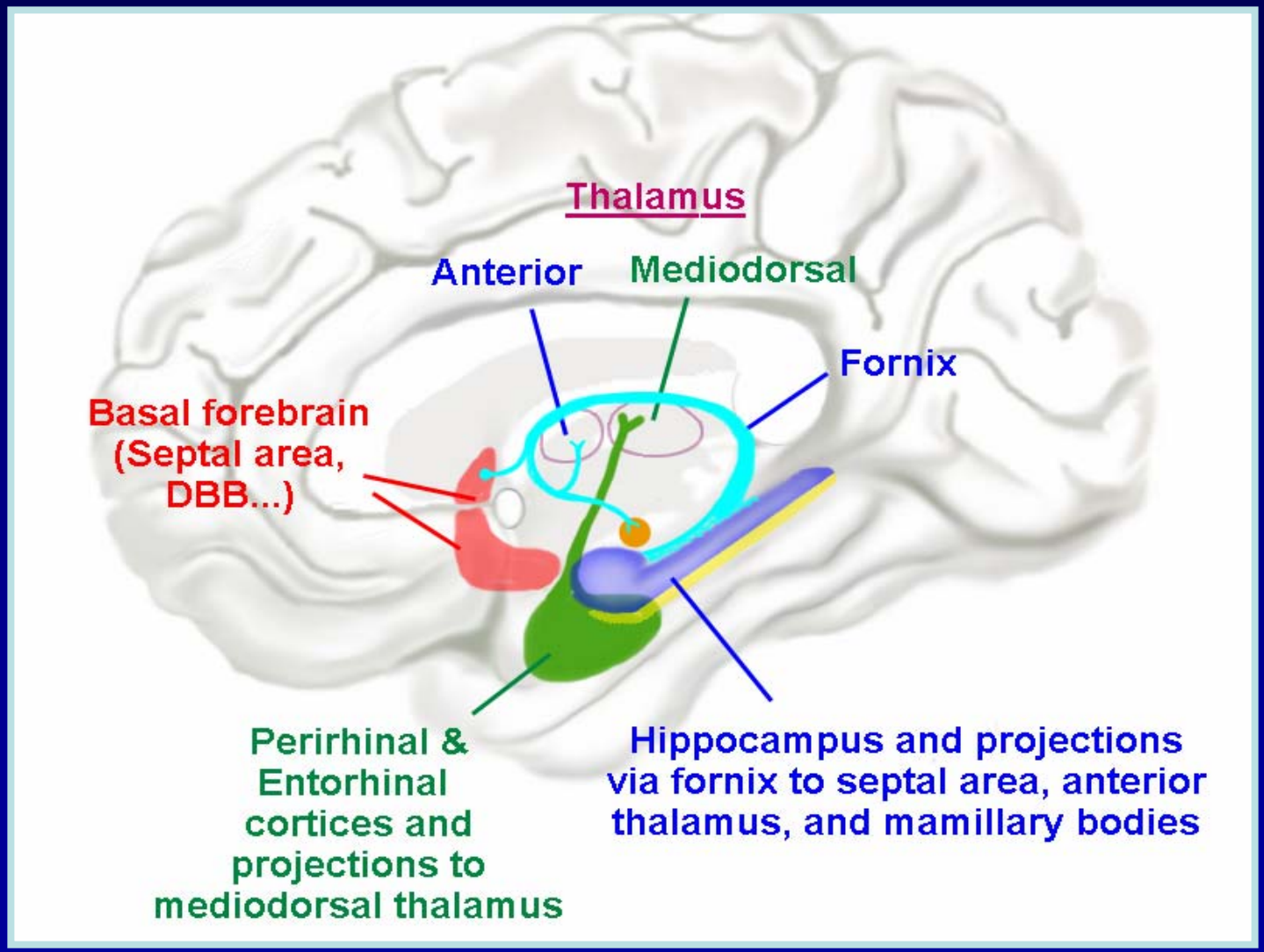
Steven James Silva (Reuters)

Memory modulation: The influence of drugs and hormones on the memory trace

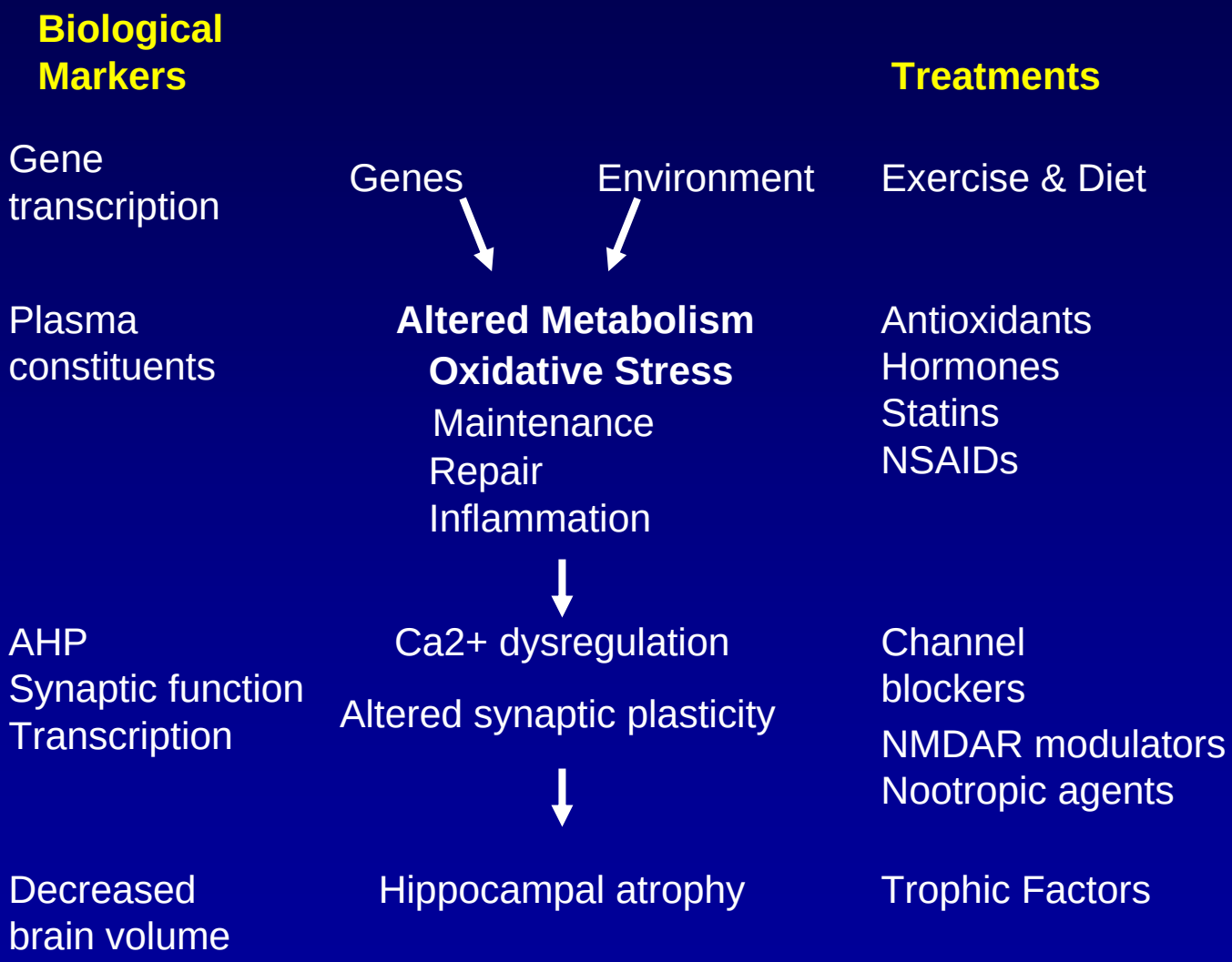


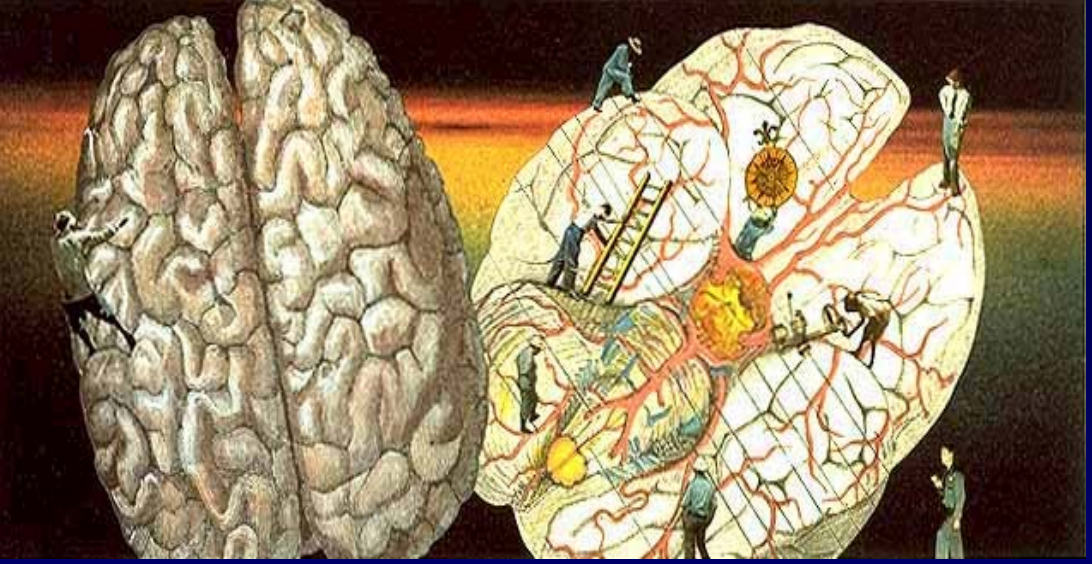
Anatomic Basis of Declarative Memory Disorder

3. Basal forebrain Alzheimer's patients and the elderly.



Pharmacological treatments designed to act directly on Ca2+ regulation are not very effective at improving memory.

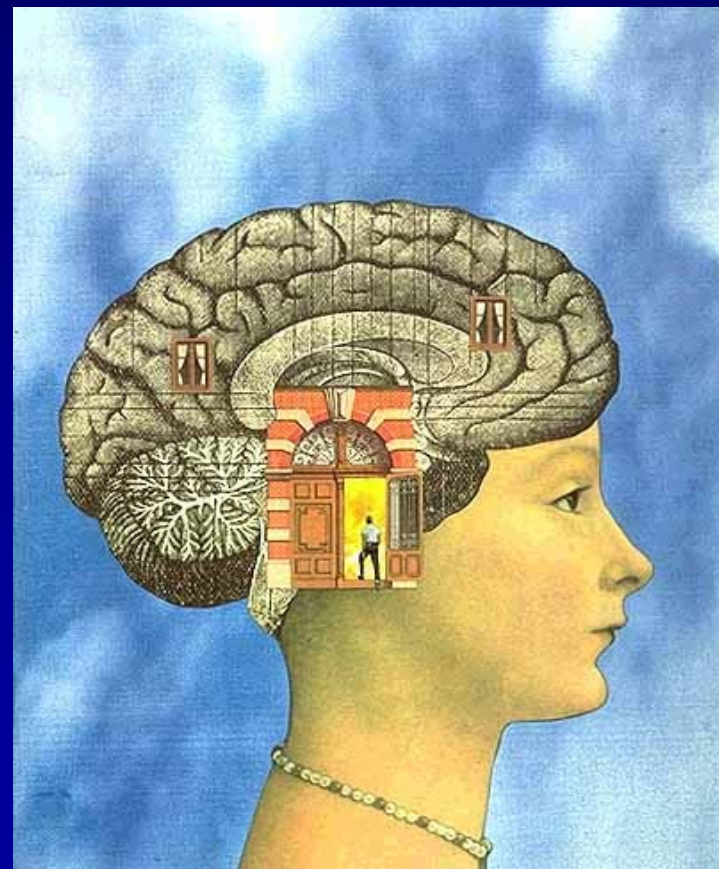


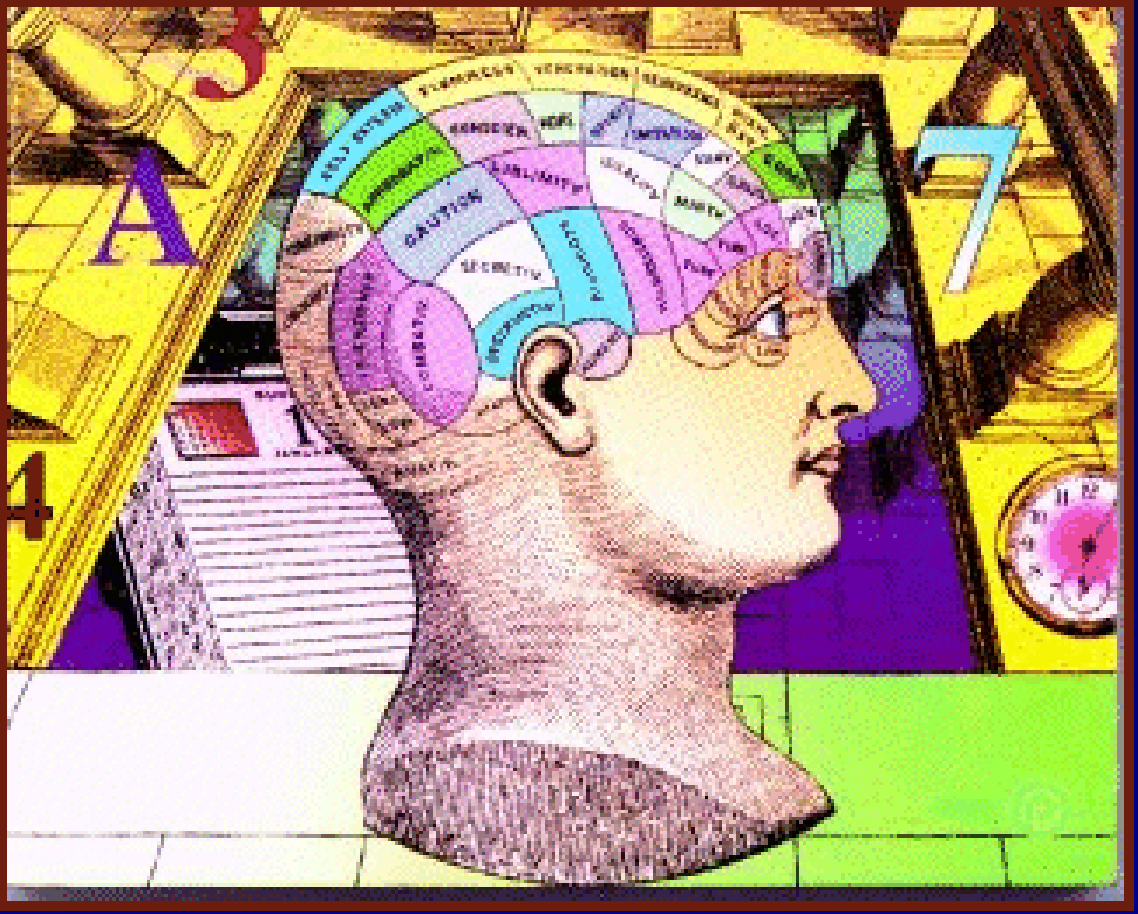


Institute on Aging
Dr. Christiaan Leeuwenburgh
Dr. Tim Hofer

Dr. Sue Semple-Rowland
Dr. Ashok Kumar
Dr. Li Cui
Dr . Chris Norris
Dr. Keith Sharrow
Dr. Heather Fugger
Kristina Aenlle

Supported by NIH grants AG14979, MH59891 and the McKnight Foundation





Where are memories stored?

Memories are stored in regions that process the specific information to be remembered and thus are distributed widely in association cortex.

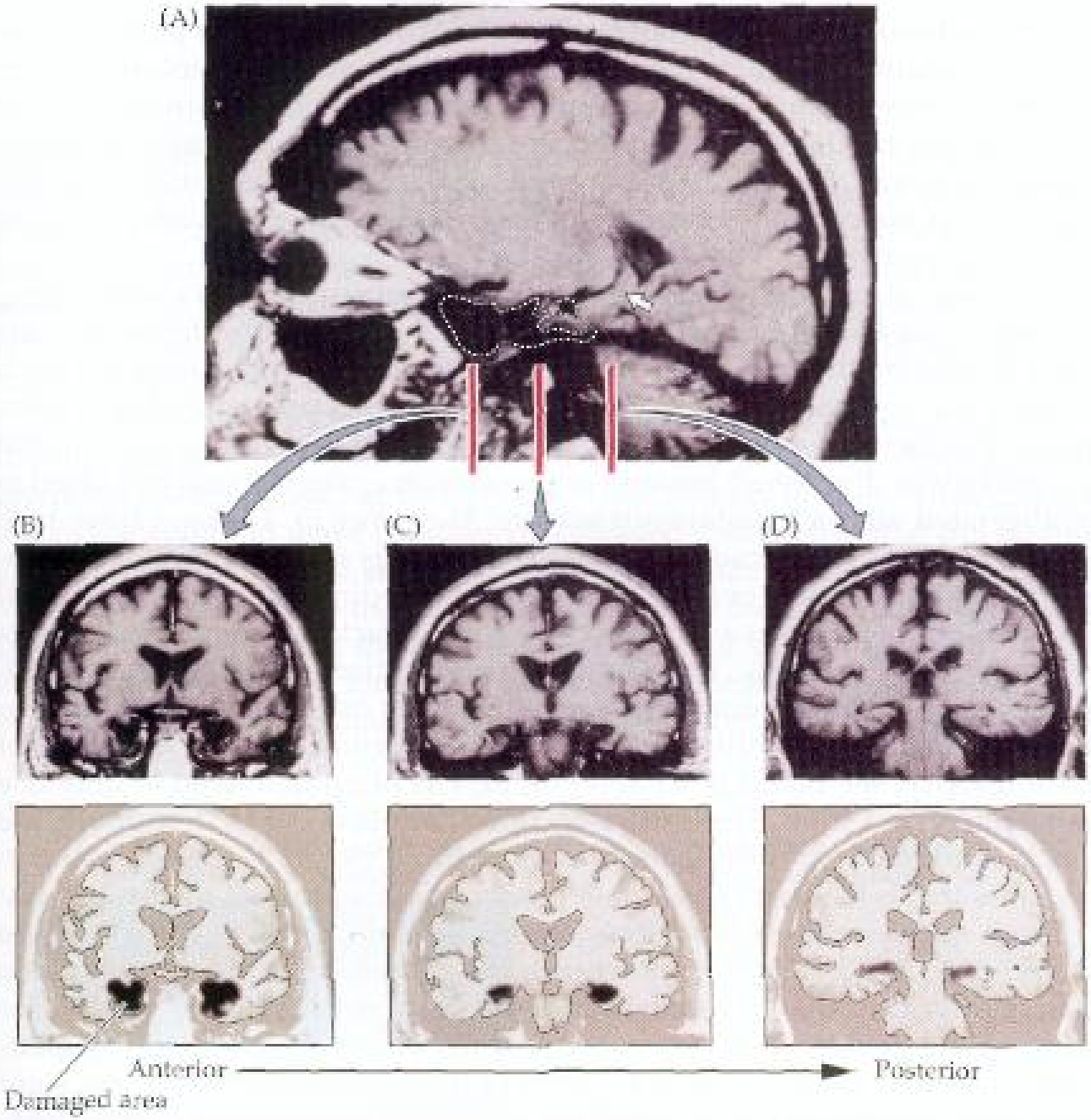
As such, focal lesions are not likely to disrupt memory as a whole.

Karl Lashley: “law of mass action”

Distinct memory systems mediating declarative, emotional and procedural memory functions

Main anatomic memory systems:

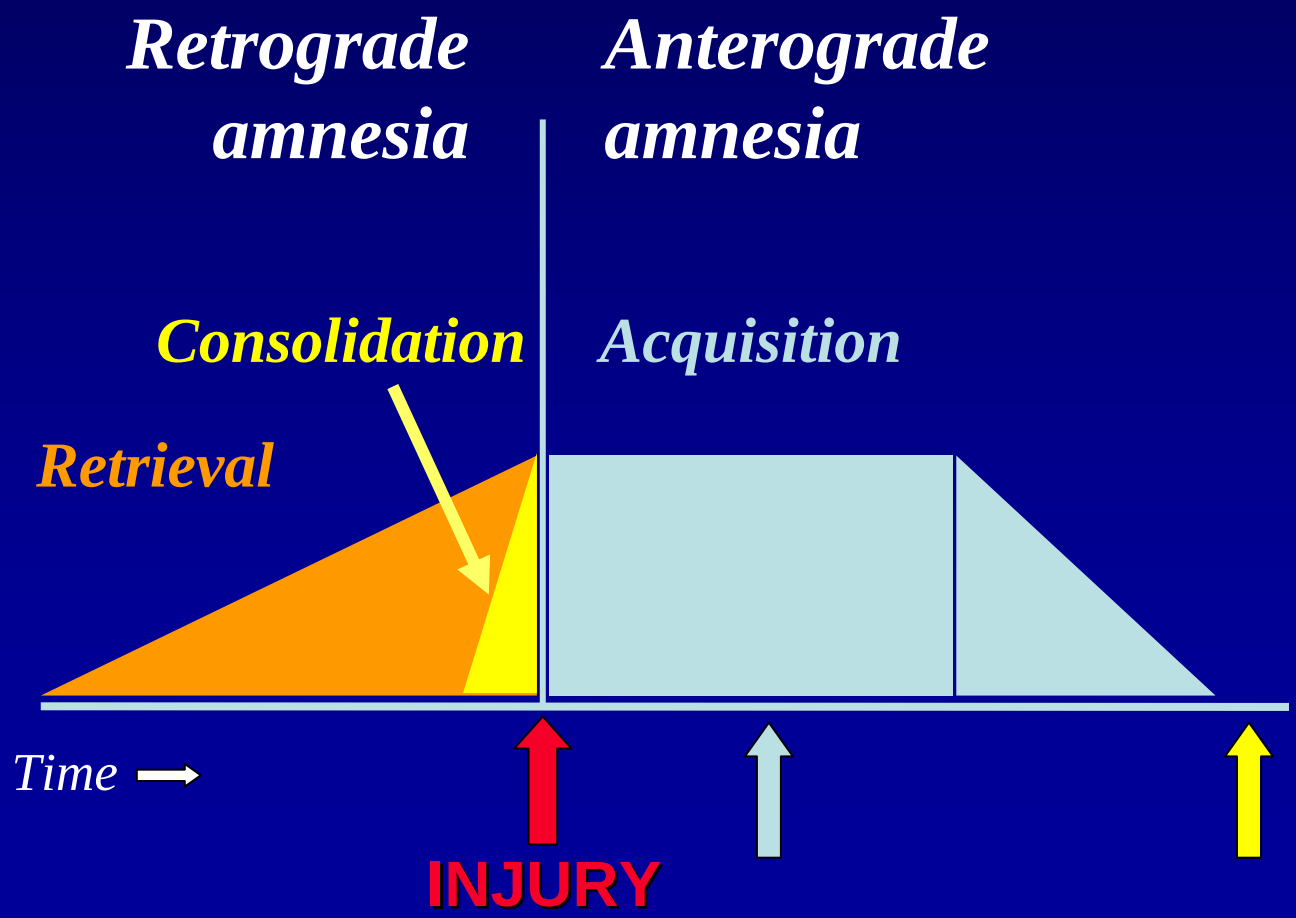
- Declarative memory; Episodic memory
- Emotional memory; fear conditioning;
- Motor conditioning;
- Skills and Priming.



MRI images of patient H.M.: Bilateral anterior lobectomy.

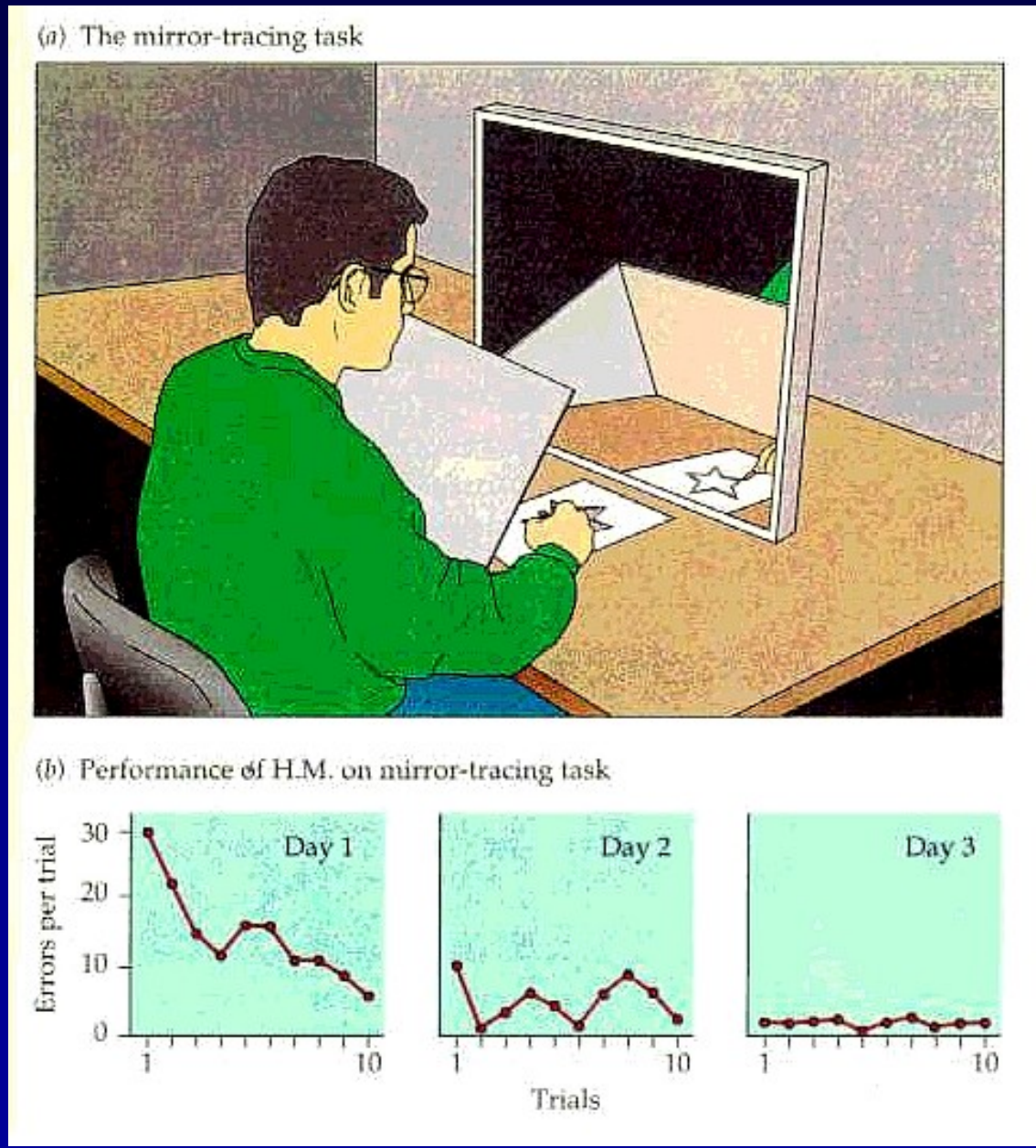
H.M.'s Memory Deficits

Minor retrograde amnesia (retro - backwards)
Normal short-term memory (digit span is normal)
PROFOUND antero (forward-acting) amnesia

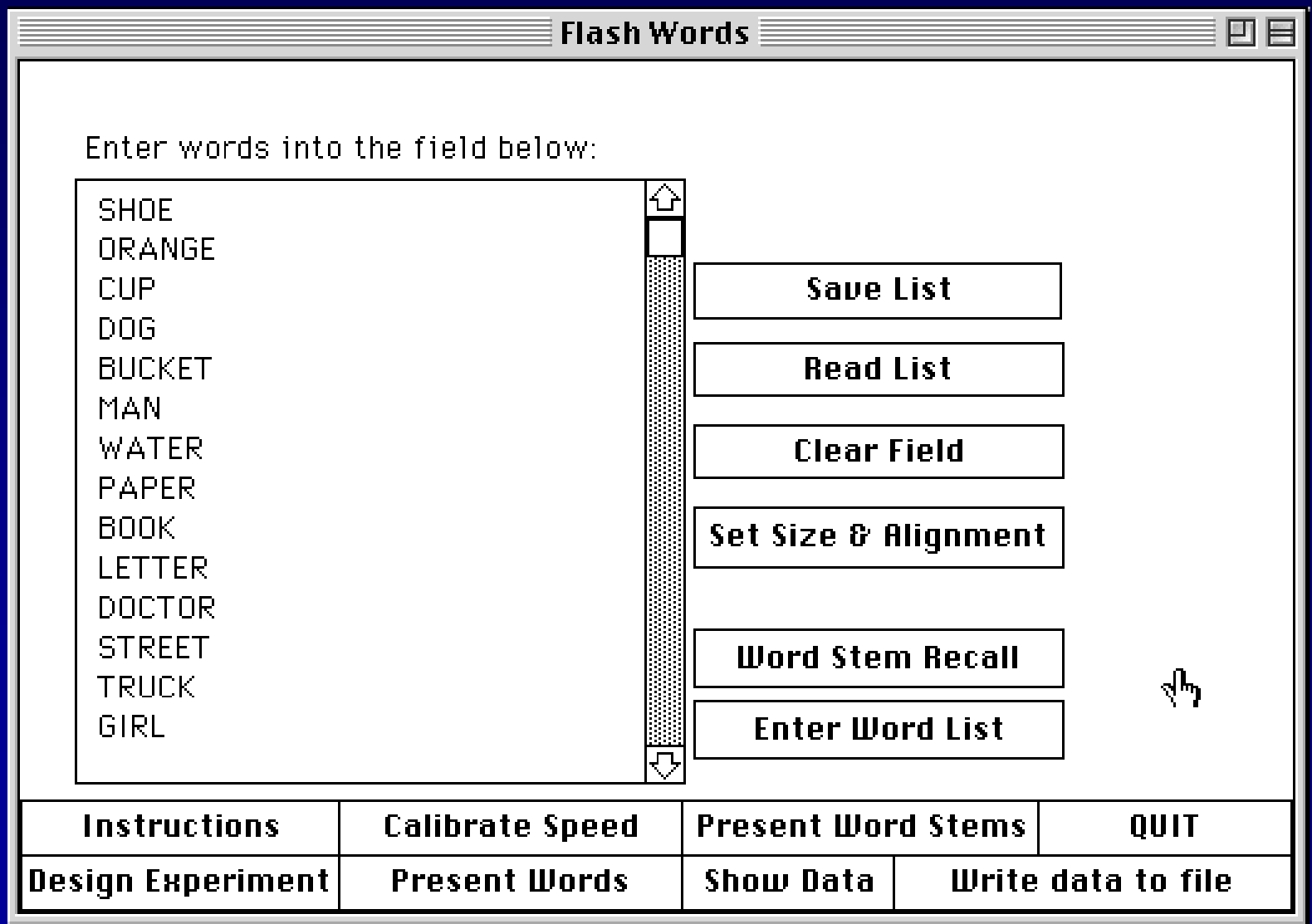


Certain memory processes were spared.

Procedural Memory (nondeclarative, implicit): throwing Frisbee, playing the piano, riding a bike; can't be accessed consciously, but can be performed without conscious recollection; take a long time to form, but not easily forgotten, motor memory.



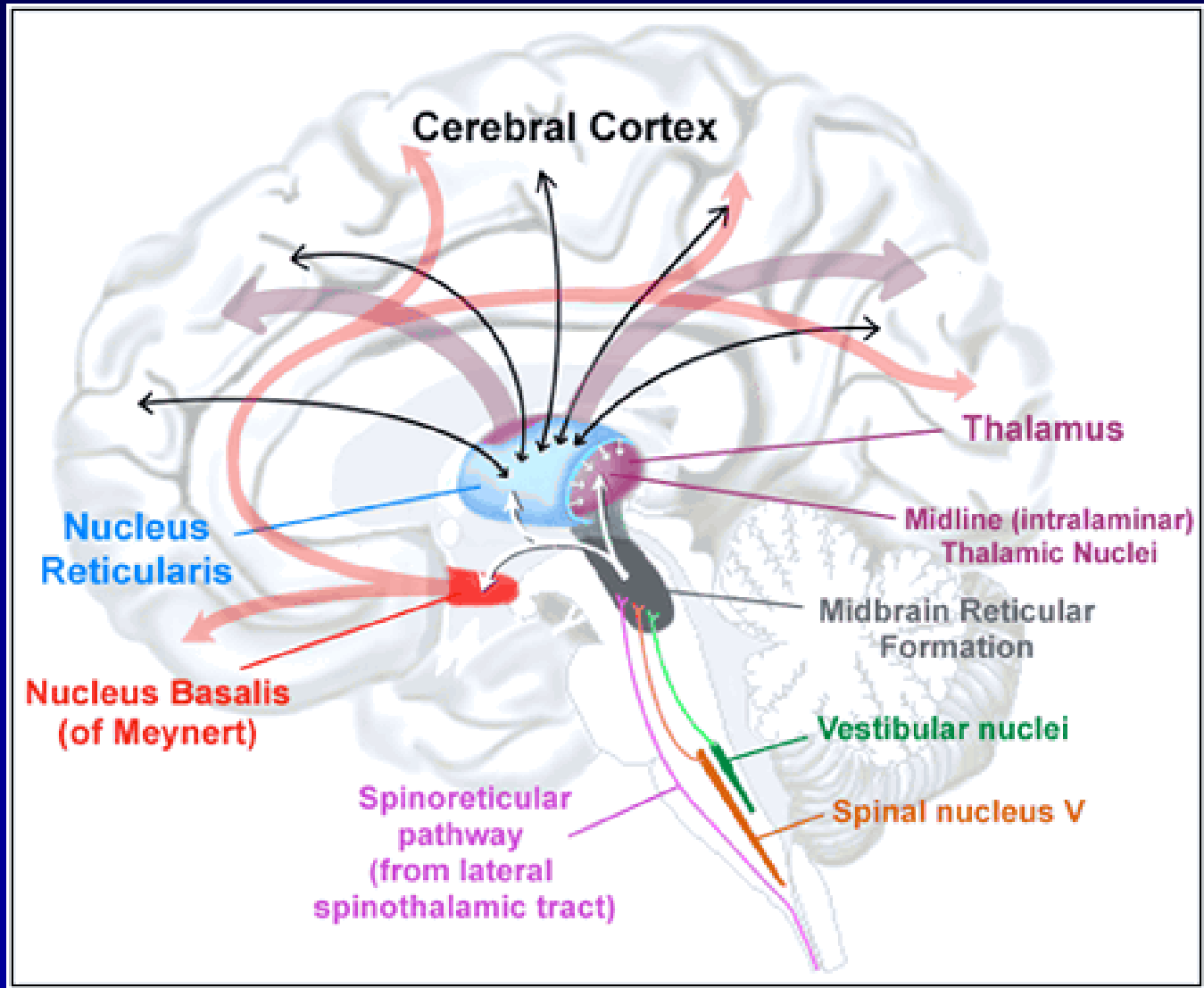
Word Priming: L_st



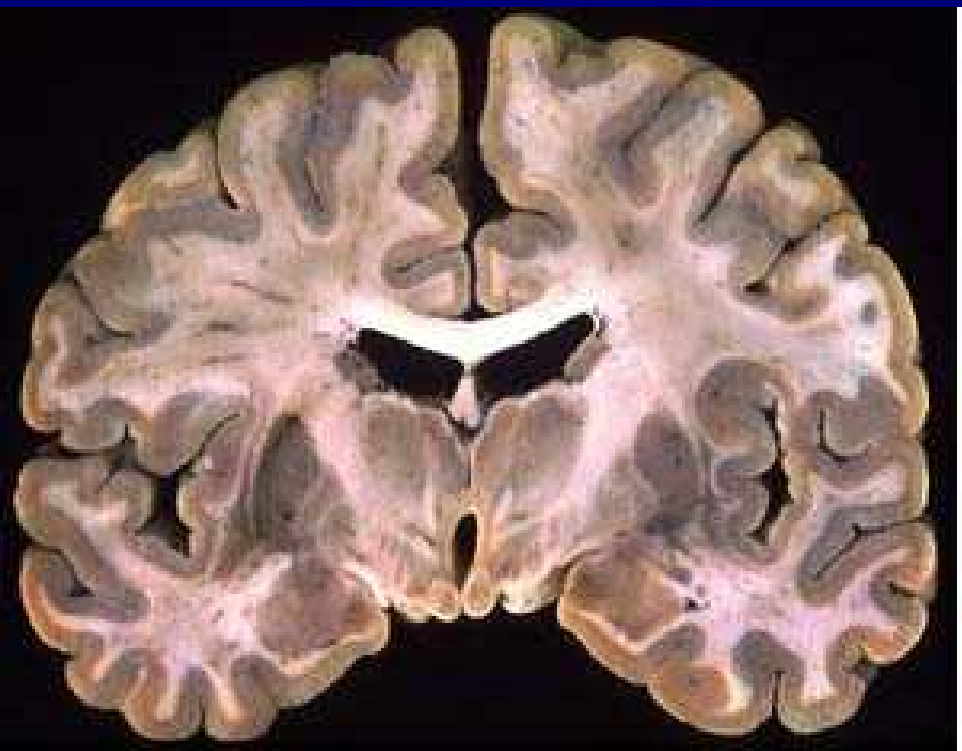
Anatomic Basis of Declarative Memory Disorder

2. Diencephalon (thalamus) patient N.A. and bilateral thalamic stroke patients.

Perhaps the best-studied individual with thalamic amnesia is the patient N.A., who has been amnestic since 1960 when he sustained a penetrating brain injury with a miniature fencing foil. The amnesia affected verbal material with no other detectable cognitive deficits. Initial CT studies showed a lesion in the left mediodorsal nucleus of the thalamus.



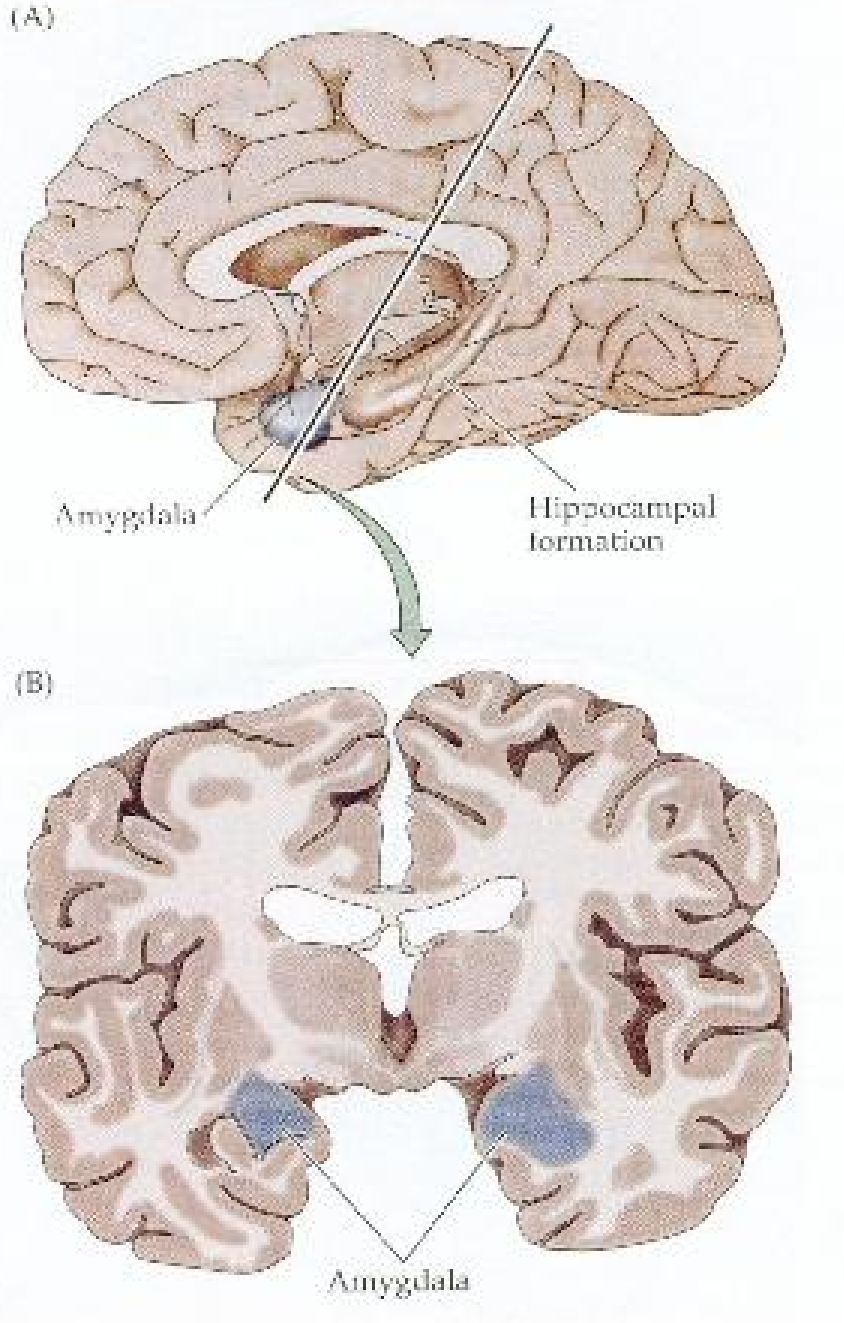
Patients with Korsakoff's Syndrome have also shown signs of amnesia. Korsakoff's syndrome is caused by chronic alcoholism which affects the **<u>mammillary bodies</u>**



Distinct memory systems mediating declarative, emotional and procedural memory functions

Main anatomic memory systems:

- Declarative memory; Hippocampus, Dorsal Medial Thalamus, Mammillary bodies, Basal Forebrain
- Emotional memory; fear conditioning; **Amygdala**
- Motor conditioning;
- Skills and Priming.



Sagittal view of the brain showing the location of the amygdaloid complex of nuclei in the temporal lobe.

Coronal section through the forebrain at the leveel of the amygdala.

(Purves et al "Neuroscience", 2nd edition, 2001, Box B, p.634)

Post-traumatic Stress Disorder